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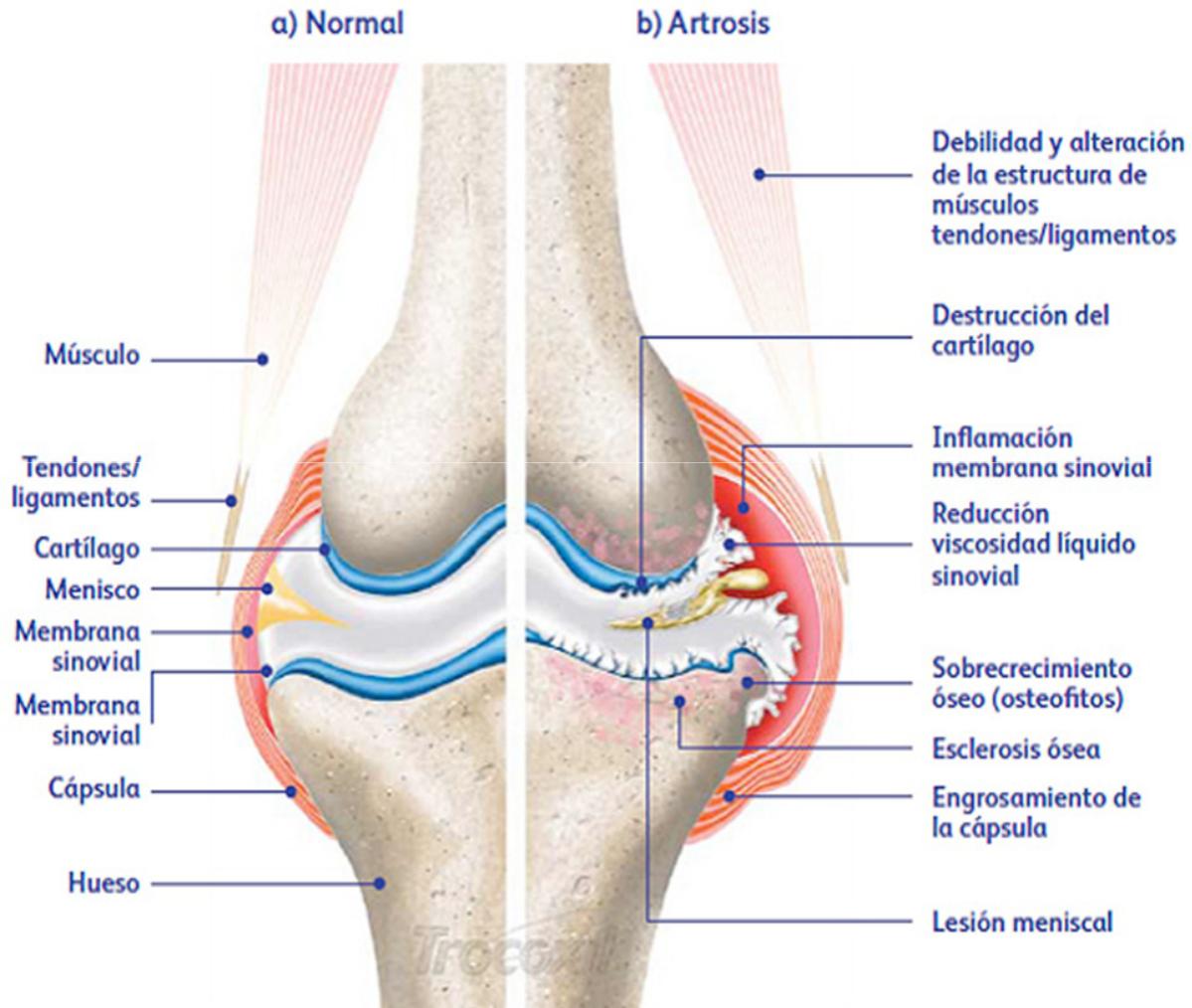
# Artrosis, pero...realmente algo se está moviendo??

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INIBIC-CHU A Coruña

# ARTROSIS

**Osteoarthritis (OA)** is a degenerative disease involving cartilage degradation; synovial inflammation; subchondral bone sclerosis; degeneration of ligaments; and, in the knee, the menisci and hypertrophy of the joint capsule. There can also be alterations in periarticular muscles, nerves, bursa, and local fat pads that may contribute to OA. The findings of pathological changes in all of the joint tissues are the impetus for considering OA as a disease of the joint, as an organ, resulting in an organic dysfunction or joint failure

# ARTROSIS



# IMPACTO EN LA SALUD

- DEGENERATIVA
- DOLOR
- RIGIDEZ
- POLIARTICULAR



- ALTA PREVALENCIA
- INCAPACIDAD FUNCIONAL
- ELEVADOS COSTES ECONÓMICOS
- DETERIORO EN LA CALIDAD DE VIDA

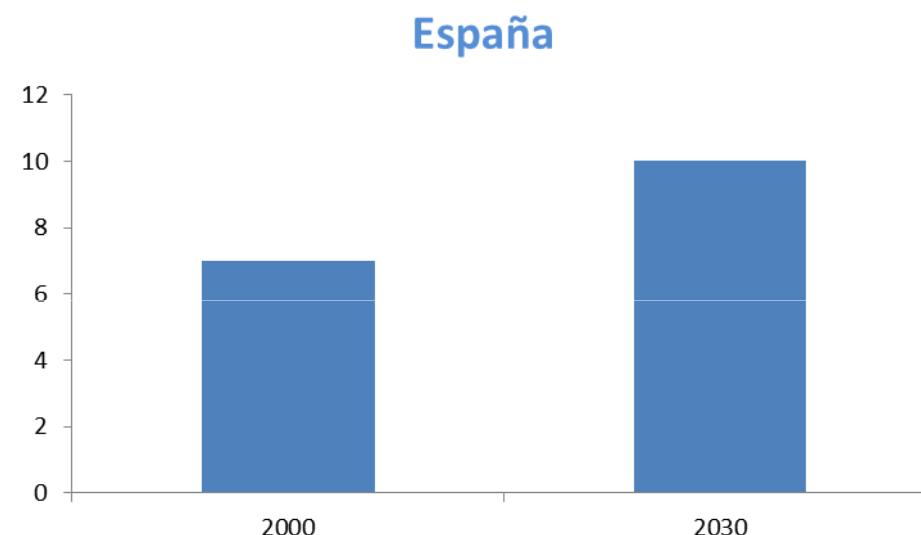
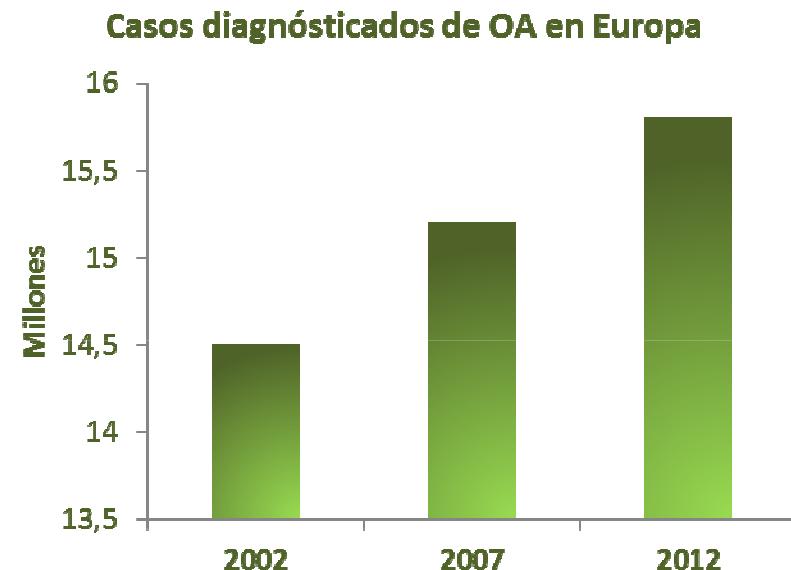
## MEDICACIÓN PALIATIVA



## PRÓTESIS

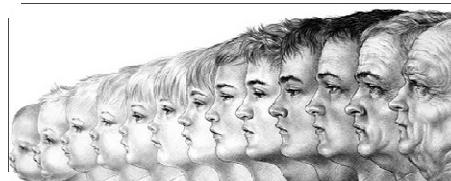


# IMPACTO EN LA SALUD



**Es importante dedicar todo tipo de recursos, humanos y económicos, para la investigación en artrosis**

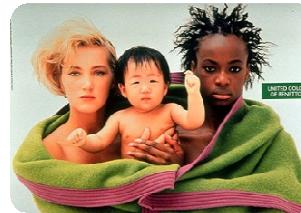
EDAD



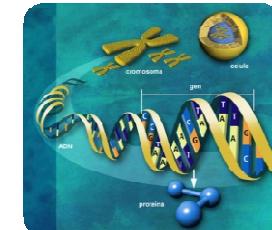
SEXO



RAZA



GENES



## FACTORES NO MODIFICABLES

TABACO



DEPORTE



## ARTROSIS

## FACTORES MODIFICABLES

PROFESIÓN



HÁBITOS DE ALIMENTACIÓN

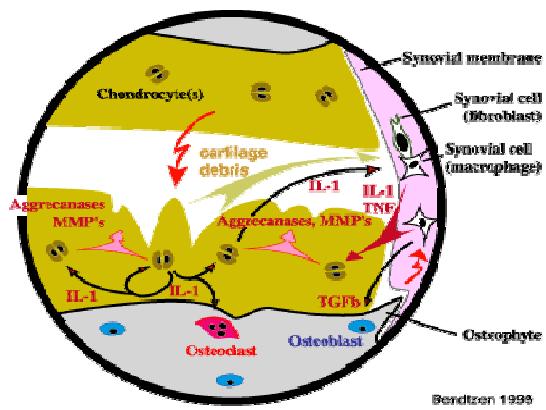


PESO



# DESAFÍOS EN LA ARTROSIS

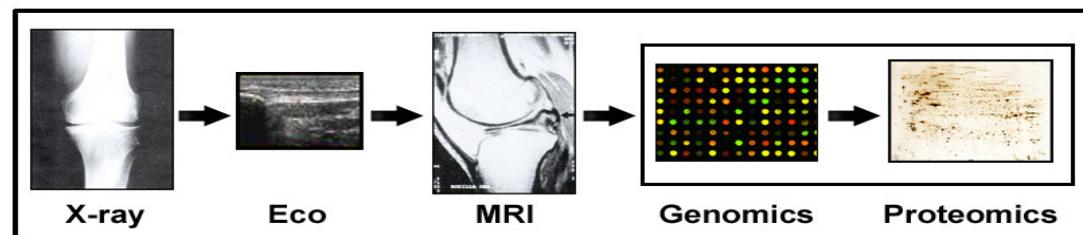
- Patogénesis



- Tratamiento personalizado



A



- Diagnóstico precoz de fenotipos de Artrosis y pronóstico: Biomarcadores

**Healthy**



**Imaging**  
XR    MRI

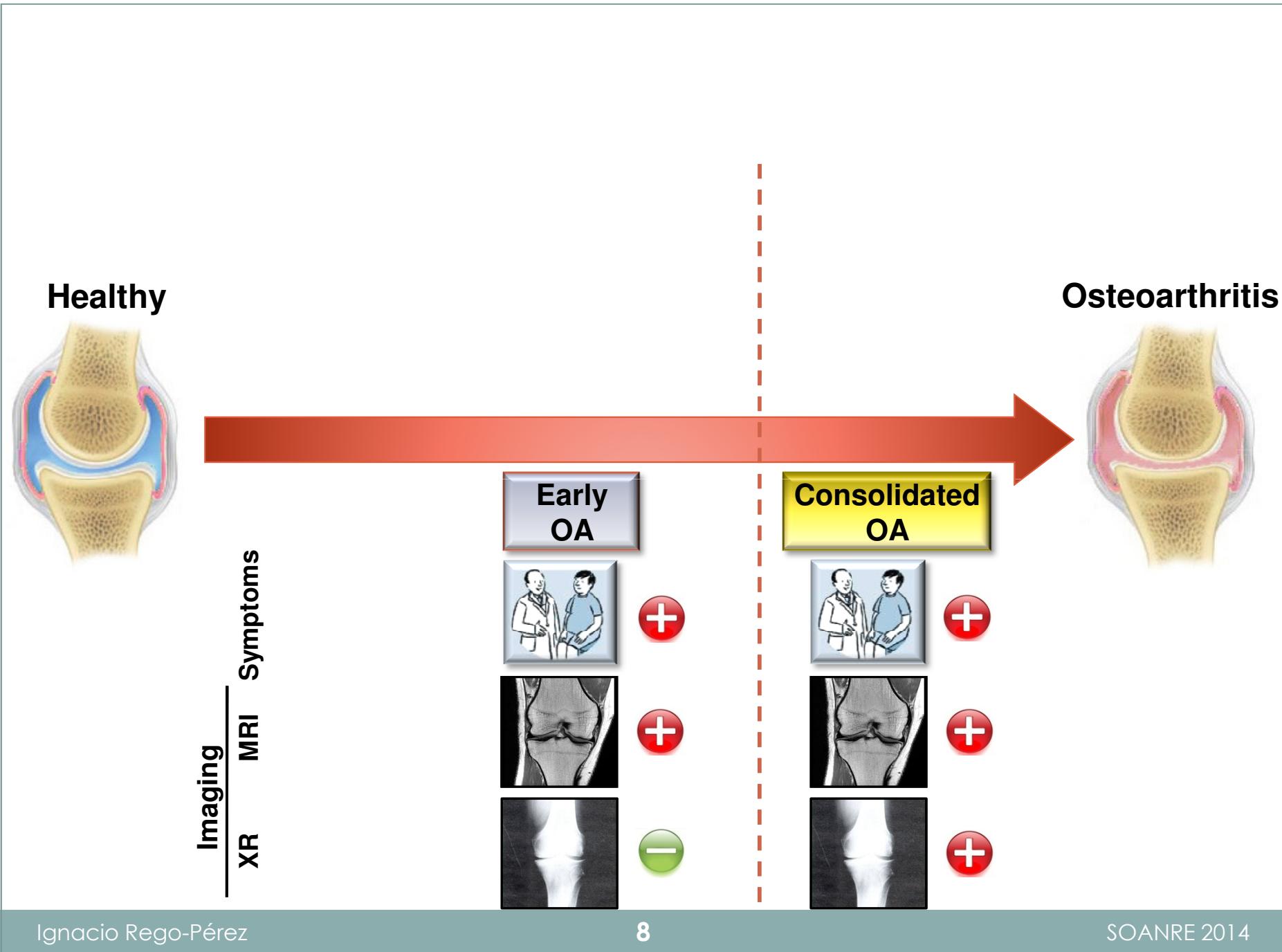


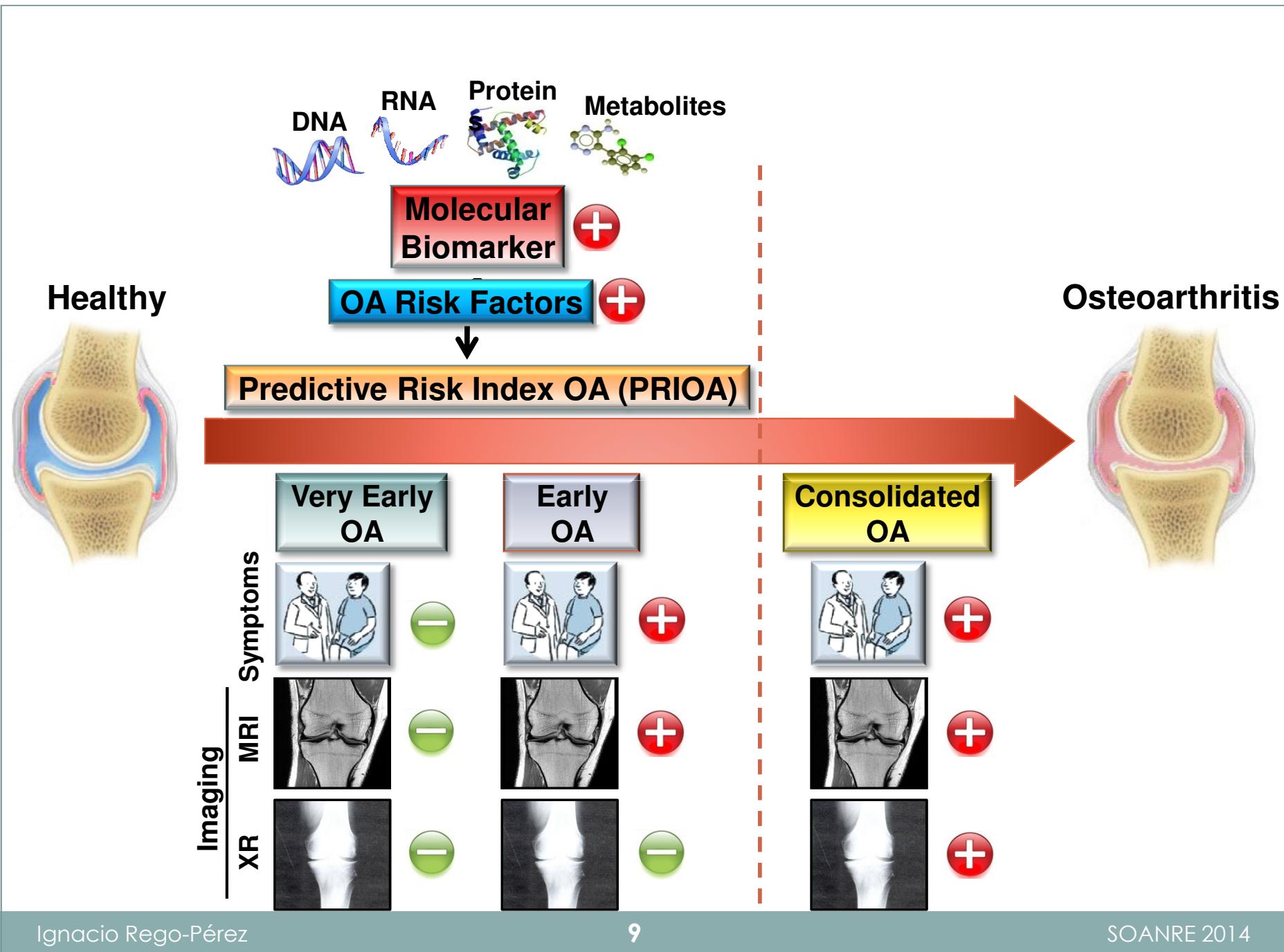
**Osteoarthritis**



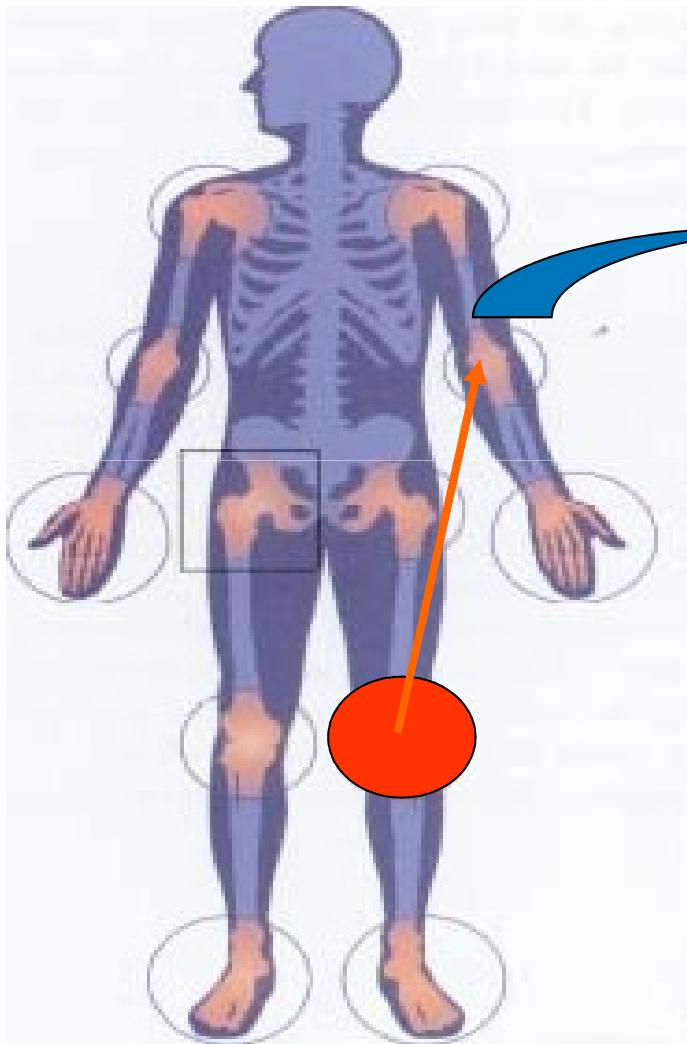
**Consolidated  
OA**







# BIOMARCADORES EN LA ARTROSIS

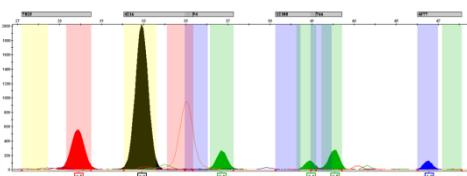


## Biomarcadores

### Proteicos

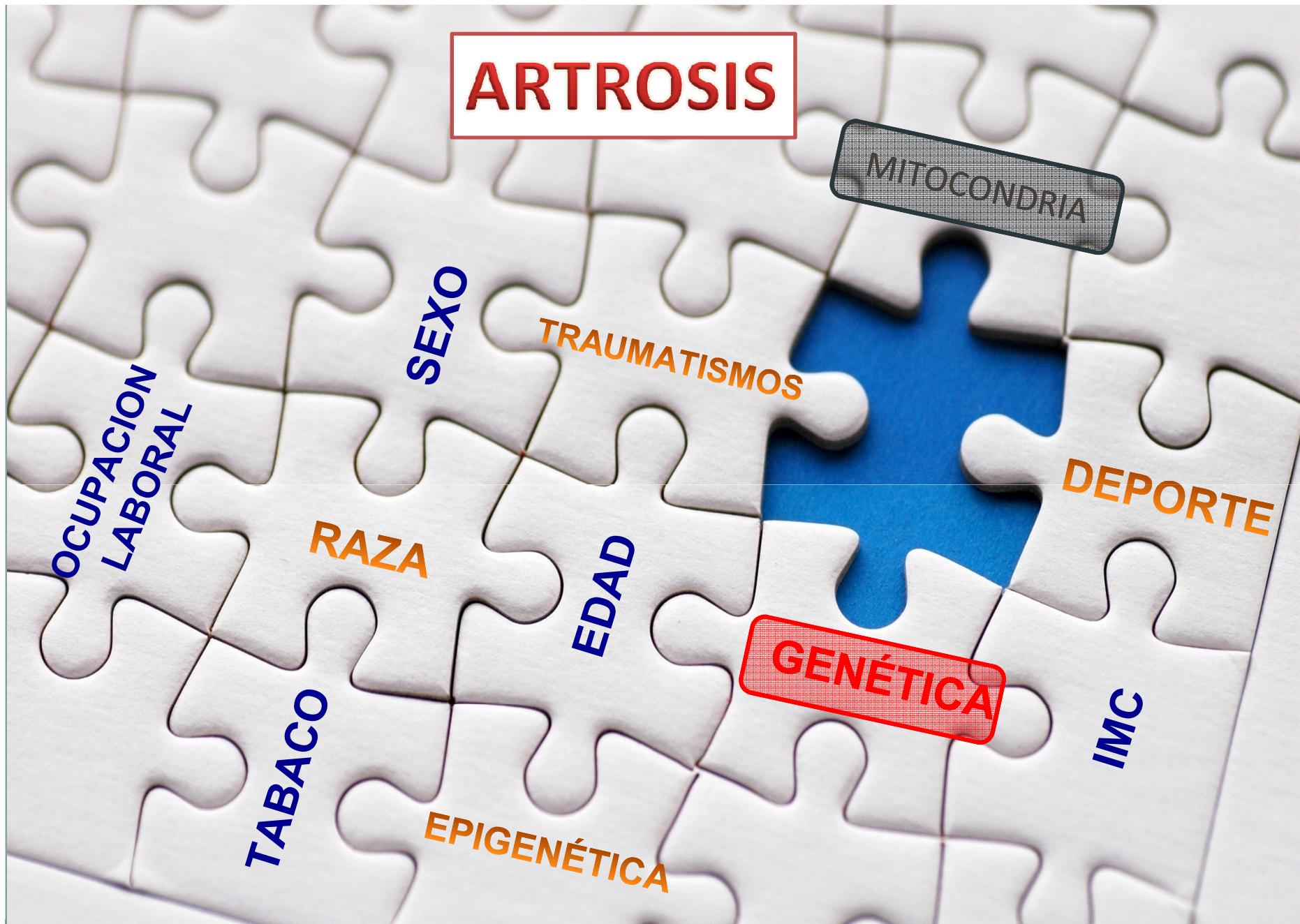


### Genéticos

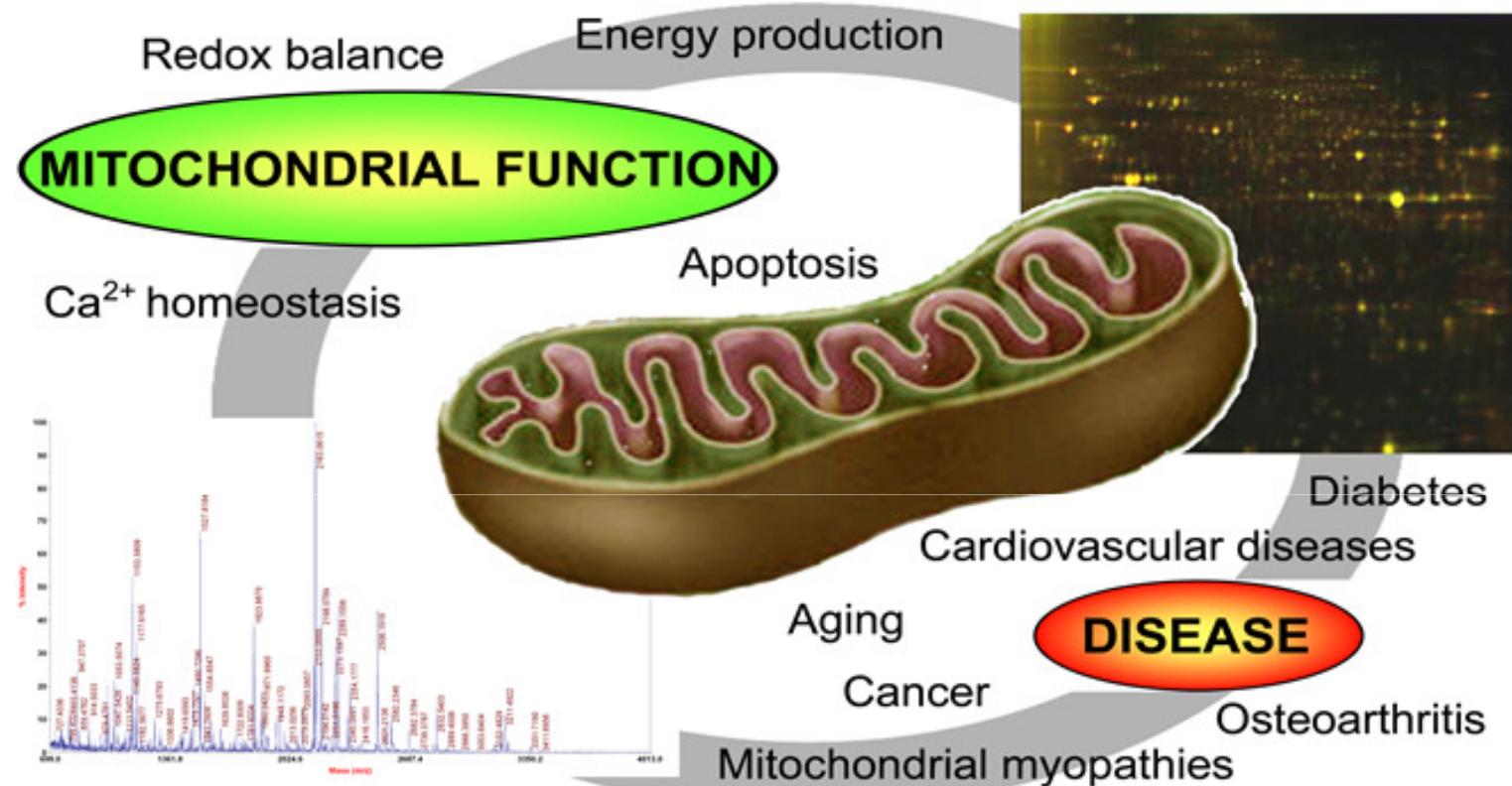


Colágeno tipo II  
Ácido hialurónico  
MMPs  
...

Haplogrupos  
mitocondriales

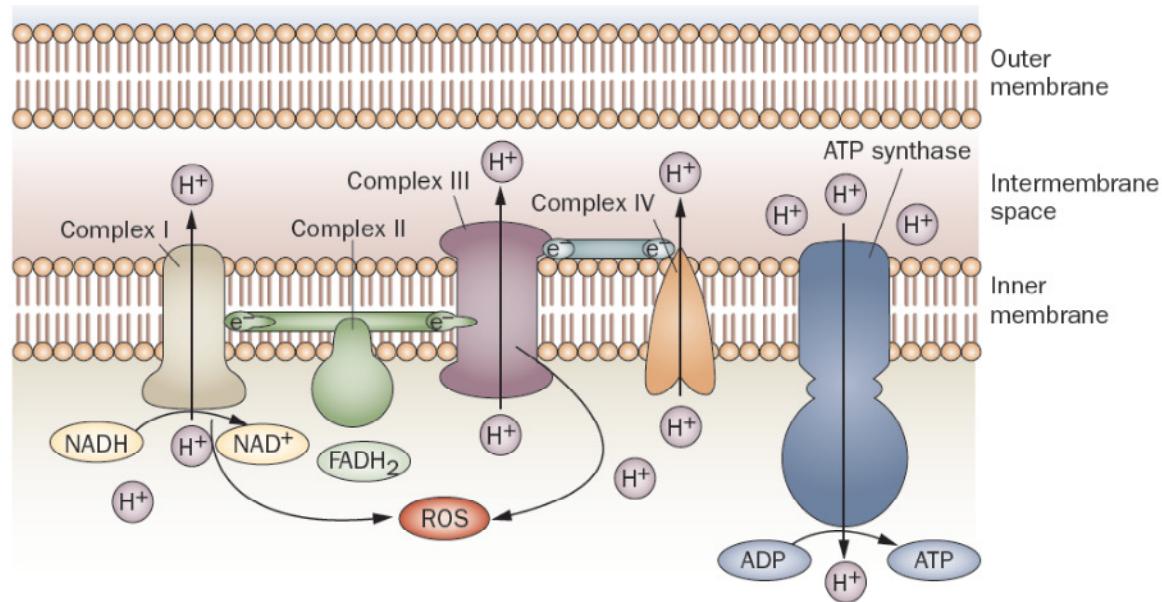
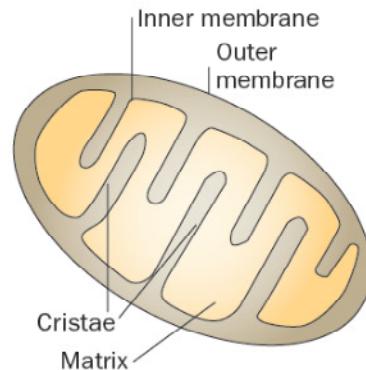


# LA MITOCONDRIA EN LA ARTROSIS



## **La disfunción mitocondrial está presente en la Artrosis**

# COMPLEJOS RESPIRATORIOS MITOCONDRIALES



1. *Proceso:* Fosforilación oxidativa.
2. *Mecanismo:* Cadena Respiratoria Mitocondrial (CRM): Cuatro complejos (I-V); Complejo V: ATP-asa

CRM dañada: ↓ ATP; ↑ ROS y despolarización mitocondrial

# DISFUNCIÓN MITOCONDRIAL EN LA ARTROSIS

**Table 1.** Values of mitochondrial respiratory chain complexes in cultures of chondrocytes from osteoarthritis (OA) patients and normal subjects\*

	Normal chondrocytes	OA chondrocytes
Age, years	66.14 ± 19.7 (21)	68.57 ± 7.66 (53)
Proteins, mg/ml	3.9 ± 1.3 (21)	3.3 ± 0.9 (53)
CS enzymatic activity, nmoles/minute/mg protein	109.7 ± 23.96 (20)	124.13 ± 29.67 (51)†
Mitochondrial complex activity‡		
Complex I	28.96 ± 16.87 (13)	22.53 ± 9.4 (46)
Complex II	14.22 ± 5.34 (16)	9.21 ± 3.34 (47)†
Complex III	53.74 ± 11.76 (18)	46.52 ± 9.79 (49)†
Complex IV	51.49 ± 13.5 (20)	53.15 ± 13.22 (49)

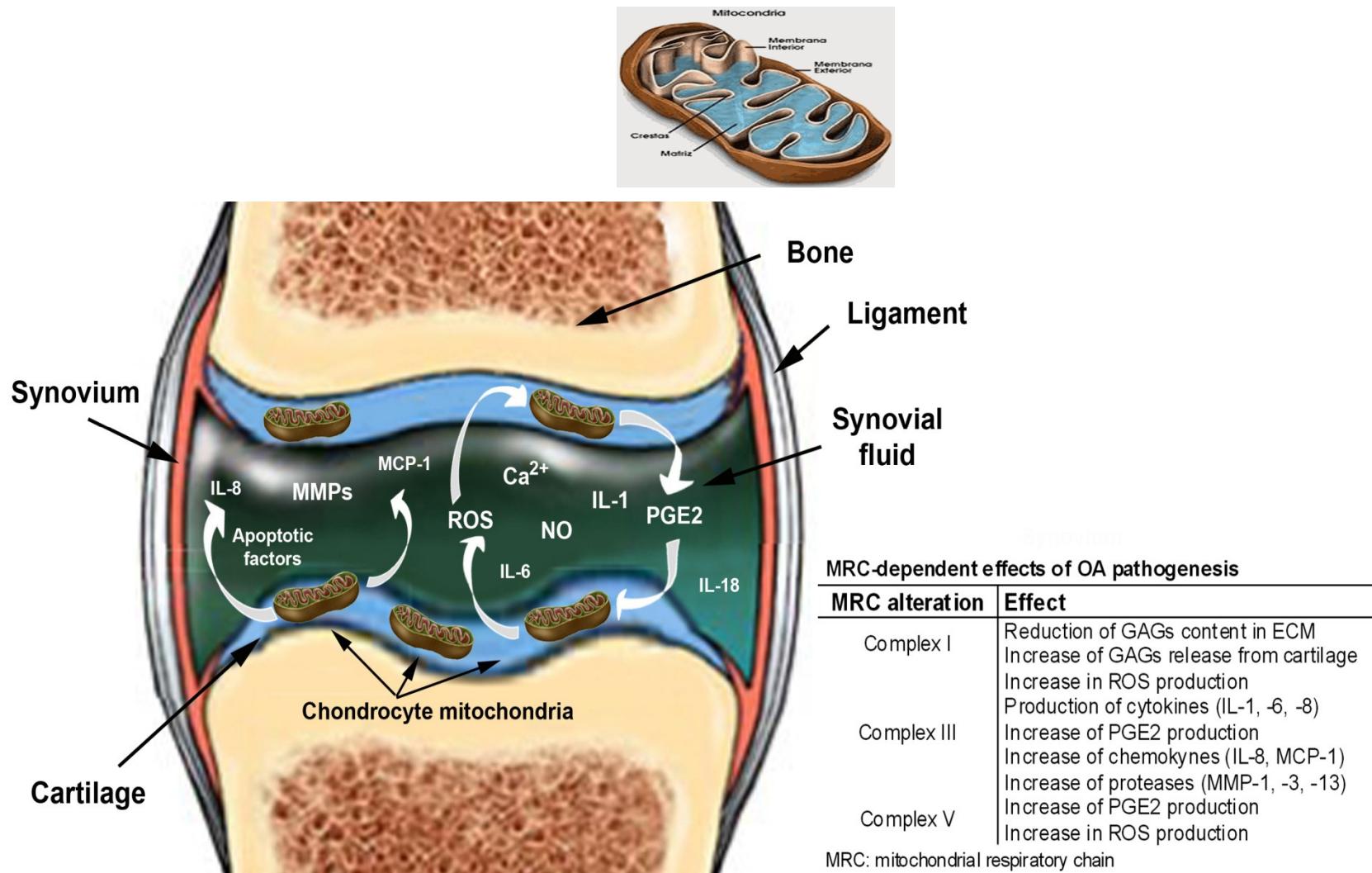
\* Values are the mean ± SD (n). CS = citrate synthase.

†  $P \leq 0.05$  versus normal chondrocytes.

‡ CS-corrected complex activity is expressed as (nmoles/minute/mg protein)/(CS specific activity) × 100. Complex I = rotenone-sensitive NADH-coenzyme Q<sub>1</sub> reductase; complex II = succinate dehydrogenase; complex III = antimycin-sensitive ubiquinol cytochrome c reductase; complex IV = cytochrome c oxidase.

Maneiro et al. *Arthritis Rheumatism* 2003

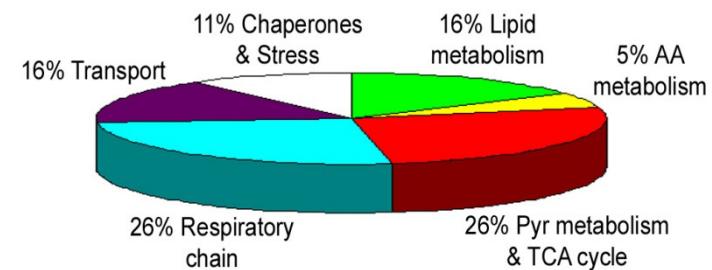
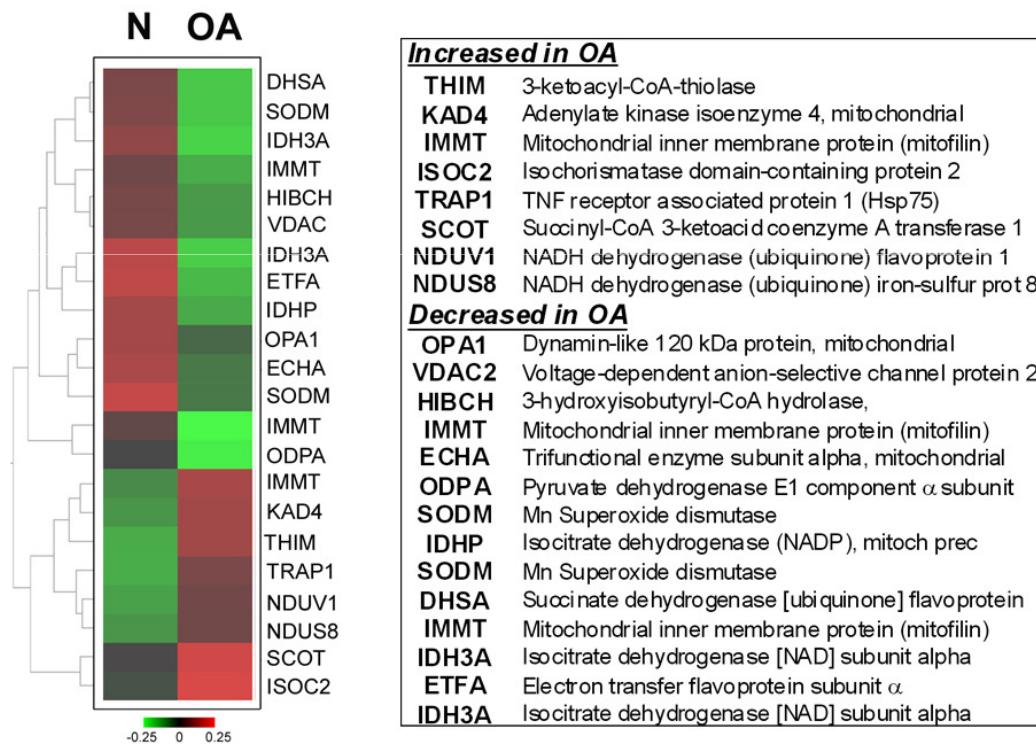
# DISFUNCIÓN MITOCONDRIAL EN LA ARTROSIS



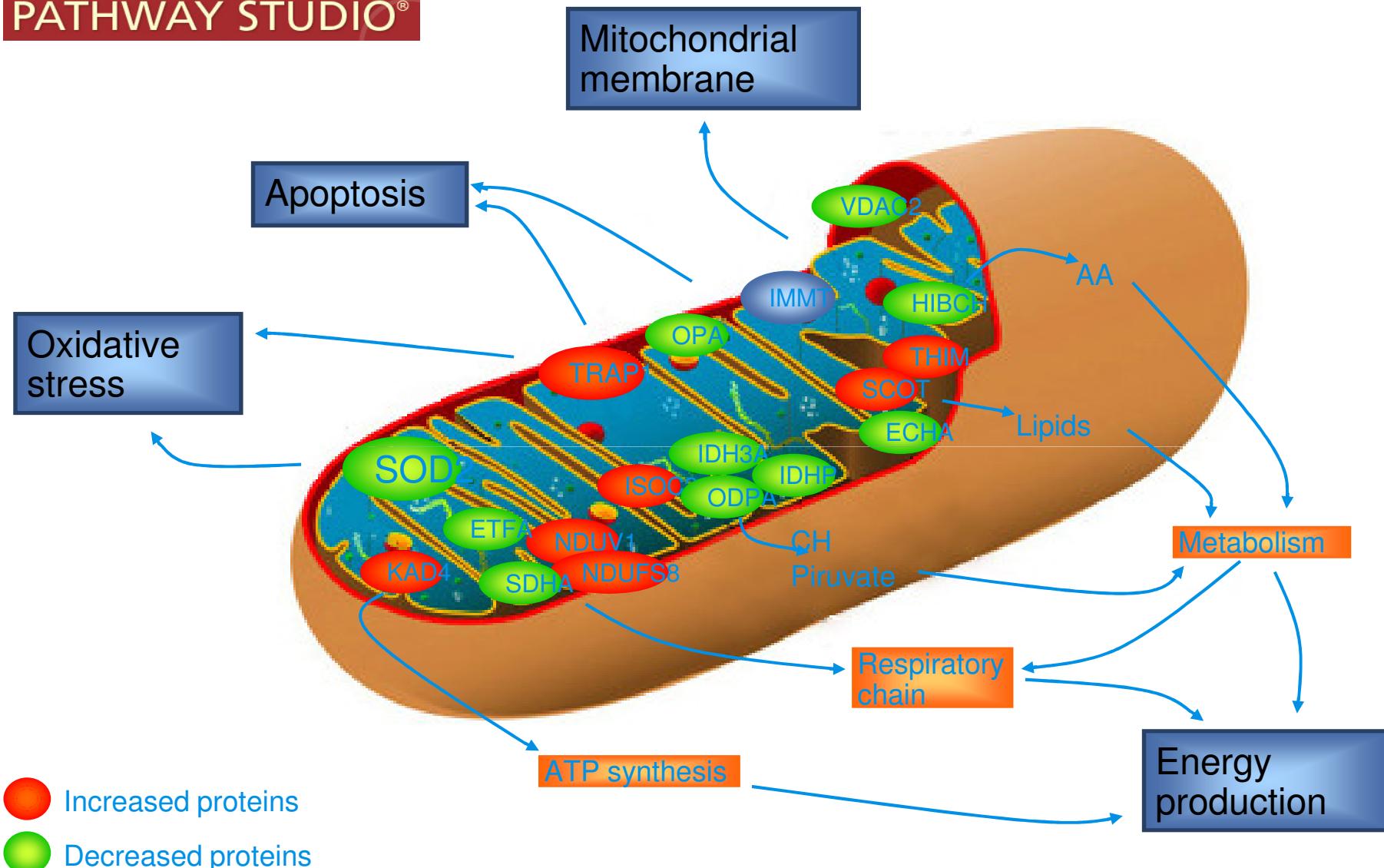
Blanco et al. *Nat Rev Rheumatol* 2011

# DISFUNCIÓN MITOCONDRIAL EN LA ARTROSIS

## List of mitochondrial proteins altered in OA

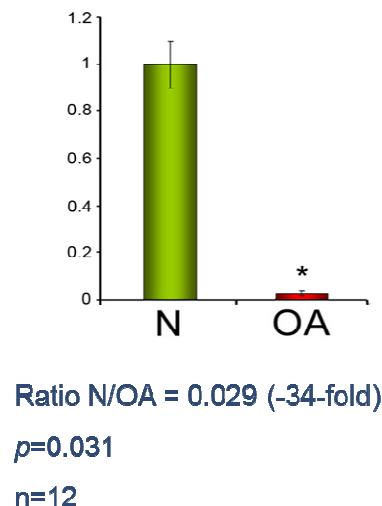


Ruiz-Romero et al. *Mol Cell Proteomics* 2009



# SOD2 EN LA ARTROSIS

Real-time PCR on cartilage



SOD2: Superóxido dismutasa mitocondrial

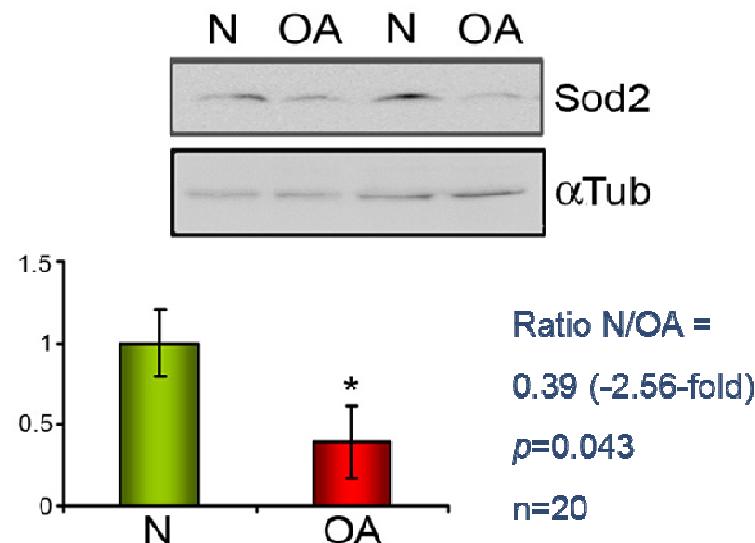
Principal enzima anti-oxidante

Protección celular frente al estrés oxidativo

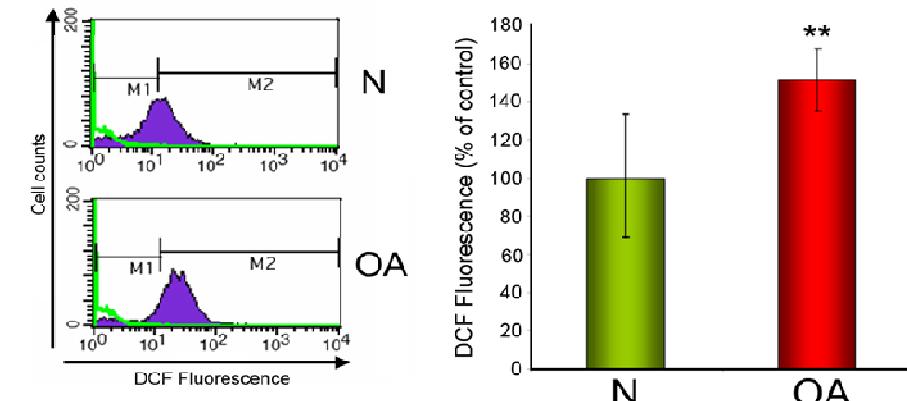
Regula el equilibrio redox de la célula

Ruiz-Romero et al. *Mol Cell Proteomics* 2009

Western blot



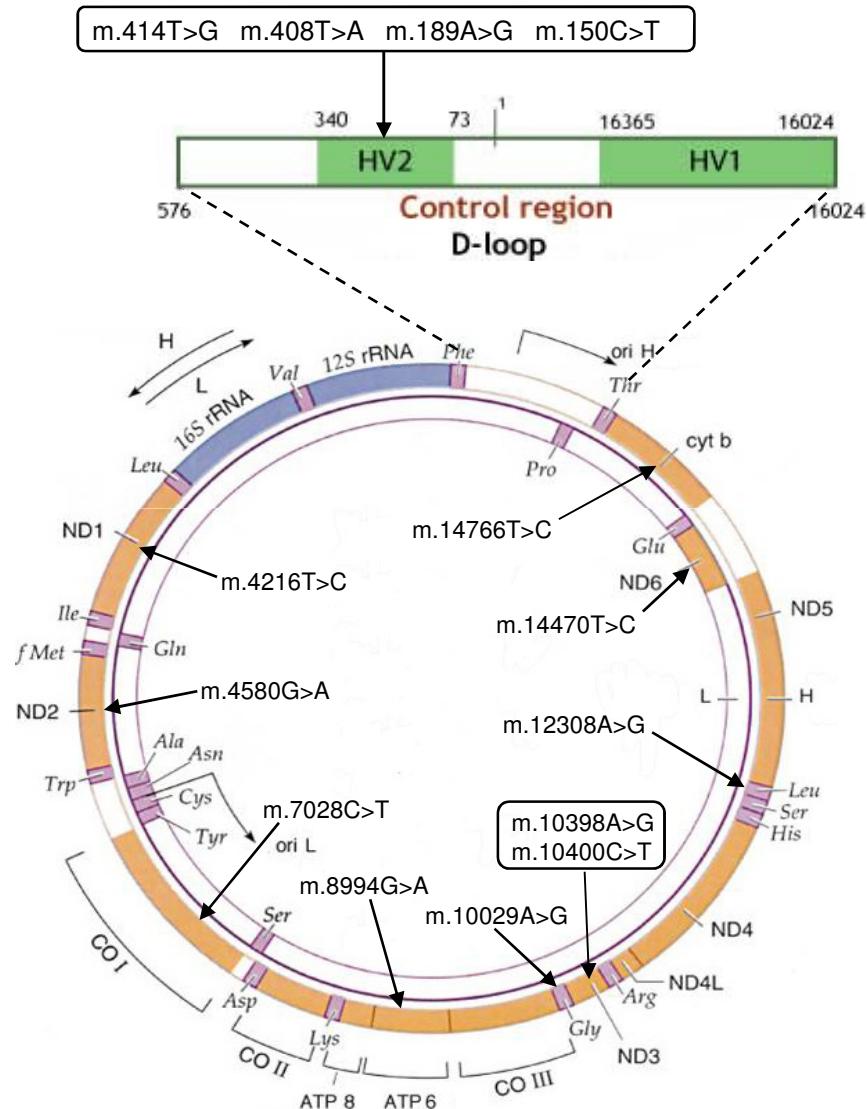
Measurement of ROS production by chondrocytes



ROS generation increases ≈ 50% in OA cells, p=0.01 (n=14)

# Pero, por qué se produce la disfunción mitocondrial?

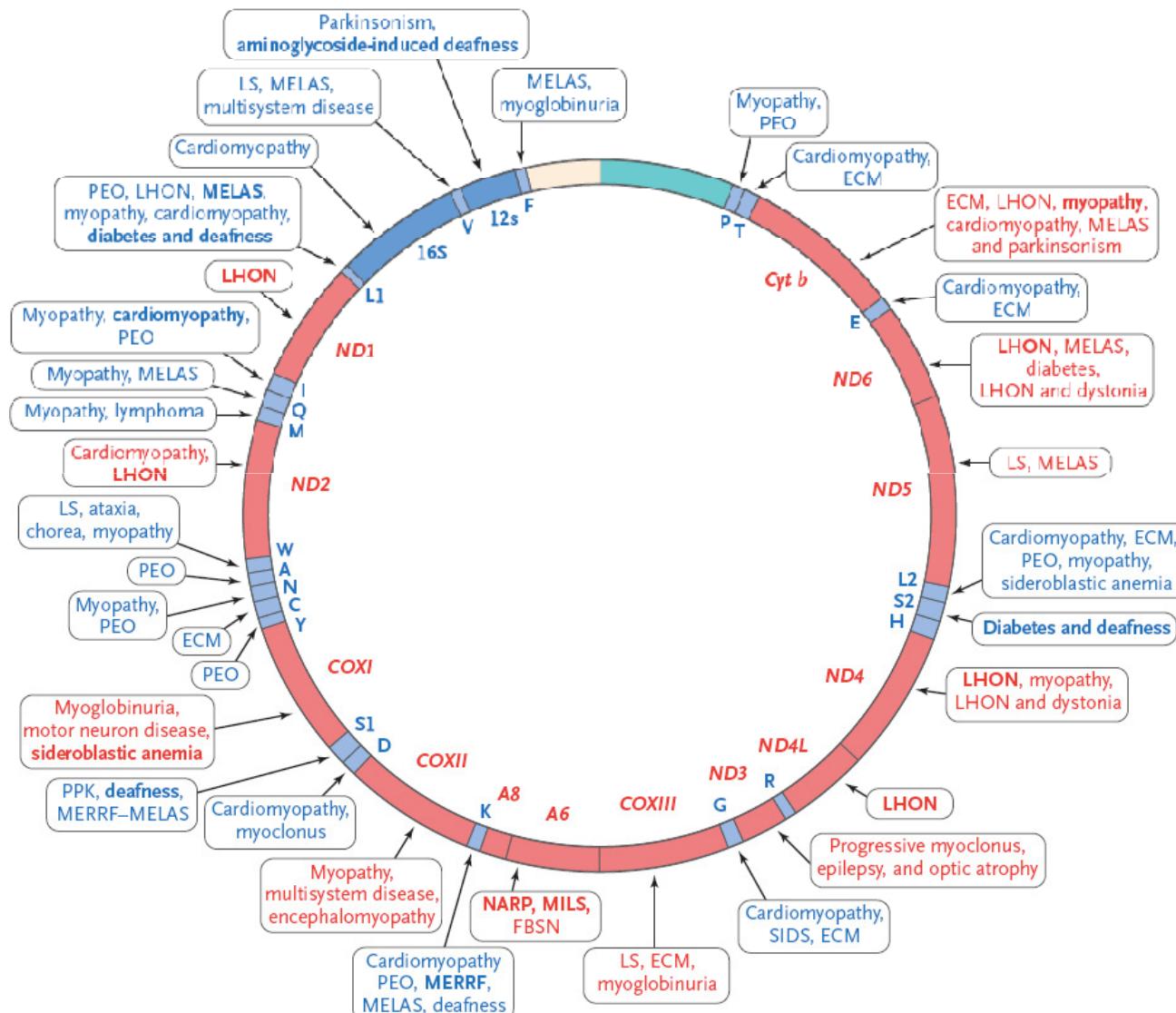
# EL ADN MITOCONDRIAL (ADNmt)



## CARACTERÍSTICAS

- Molécula circular de 16,569 pb
- Codifica para 37 genes mitocondriales:
  - ✓ 13 péptidos esenciales de la cadena respiratoria mitocondrial
  - ✓ 22 RNAs de transferencia
  - ✓ 2 RNAs ribosómicos (12S y 16S)
- Herencia materna
- Escasa recombinación
- **Alta tasa de mutación**
  - ✓ Mecanismos de reparación deficientes
  - ✓ Ausencia de histonas
  - ✓ Alta exposición a ROS
- Cada célula presenta entre 1000 y 10.000 copias

## PATOLOGÍAS ASOCIADAS A POLIMORFISMOS EN EL ADN MITOCONDRIAL

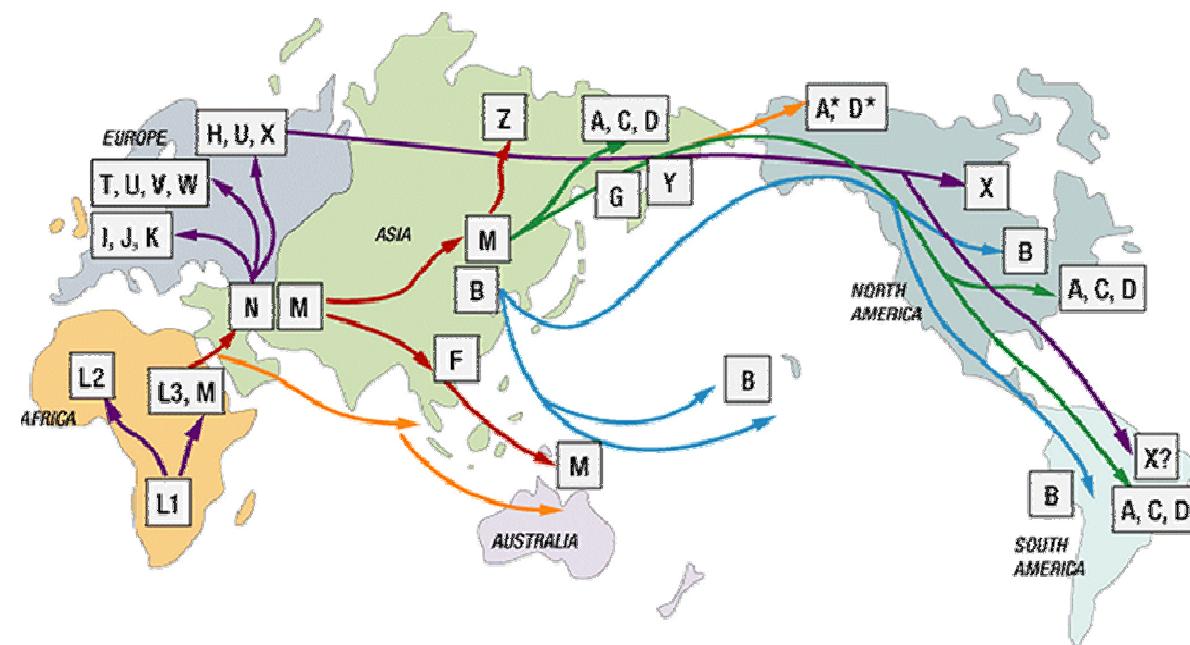


# HAPLOGRUPOS MITOCONDRIALES

- Grupos de secuencias de ADNmt definidas por la existencia de **sitios polimórficos estables** en diferentes regiones del propio ADN mitocondrial
- Acumulación secuencial de mutaciones a lo largo de diferentes linajes maternos, los cuales han ido divergiendo a medida que las poblaciones colonizaban diferentes regiones geográficas, sufriendo un proceso de adaptación climática
- Son una consecuencia directa de la herencia materna y la alta tasa de mutación del ADNmt
- Son continente-específicos

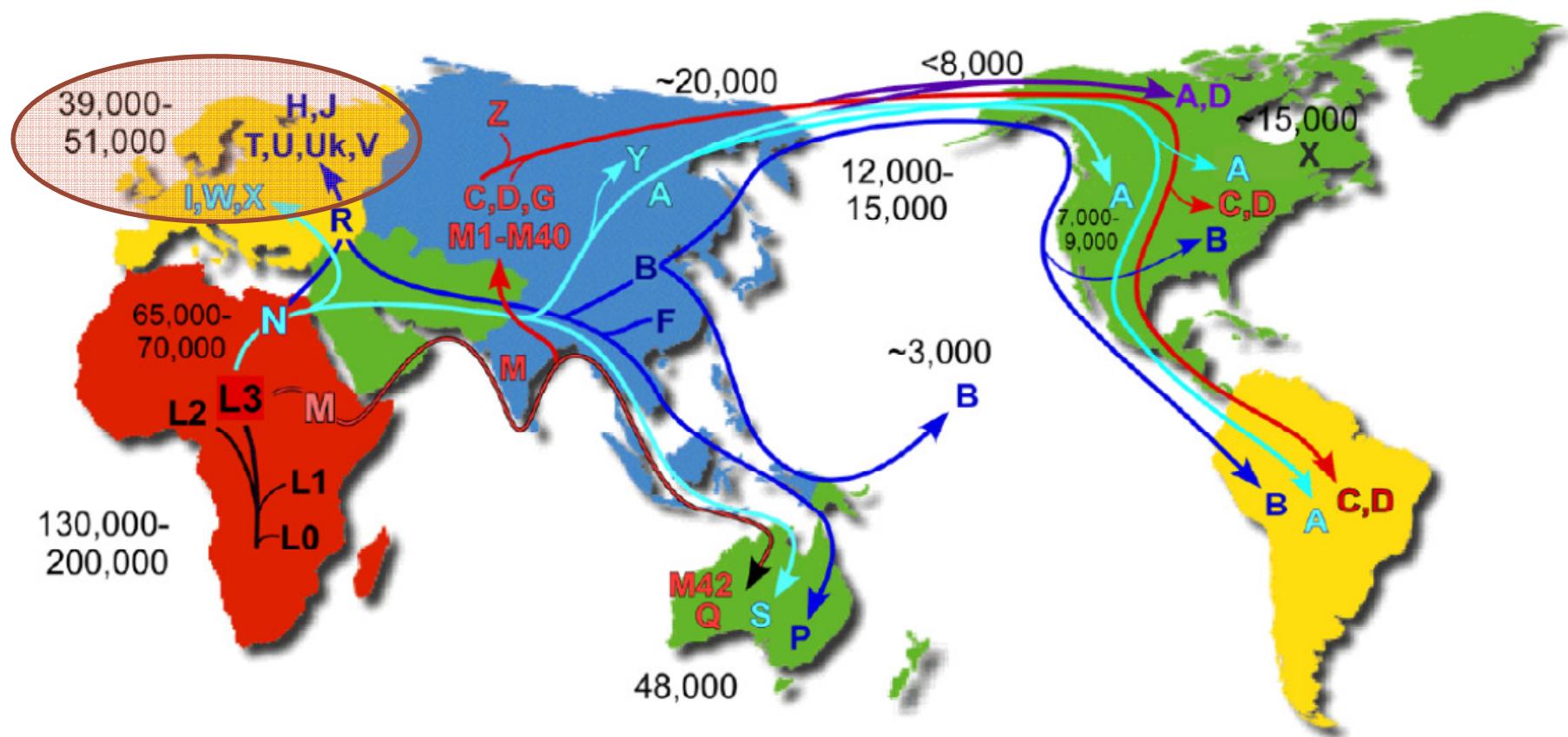
## PATOLOGÍAS RELACIONADAS CON LOS HAPLOGRUPOS

Leber  
Cardiopatías  
Encefalopatías  
Sordera  
Parkinson  
Alzheimer  
Artrosis



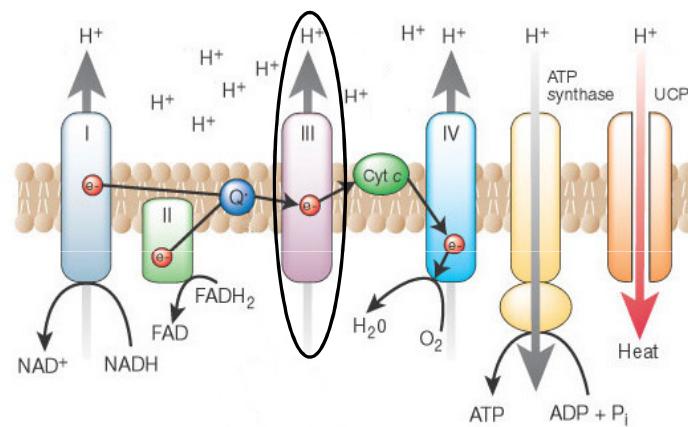
# Human mtDNA Migrations

from <http://www.mitomap.org>



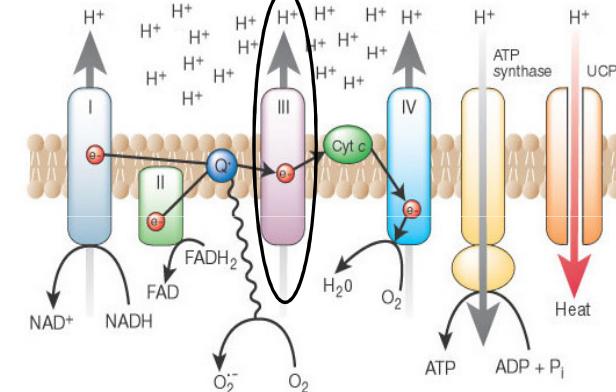
# Adaptación Climática de la mitocondria

## Zonas Frios



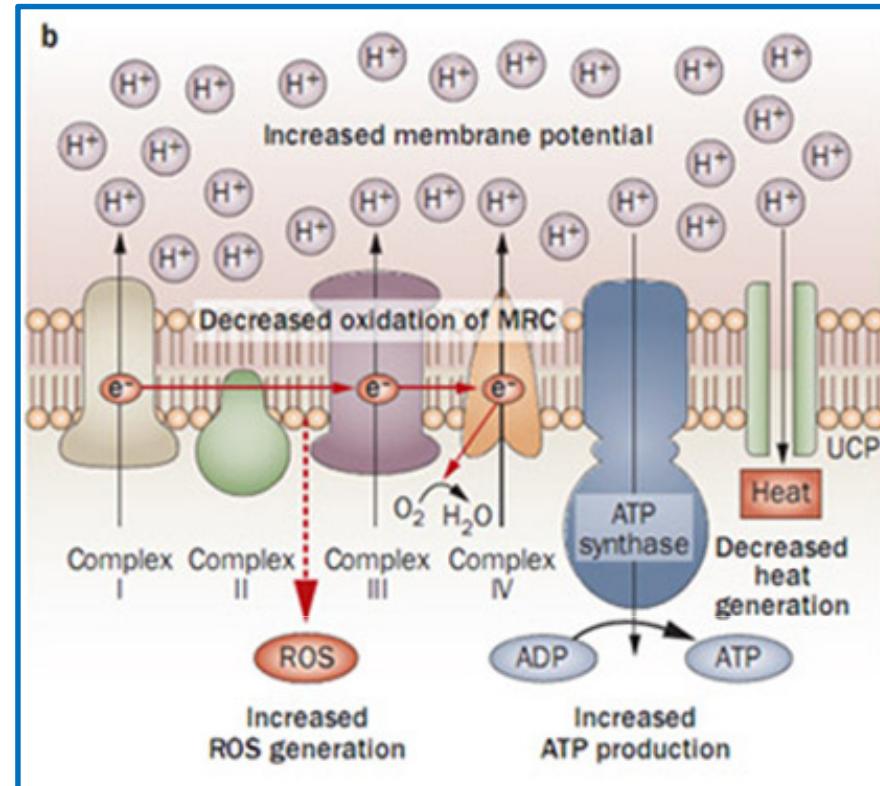
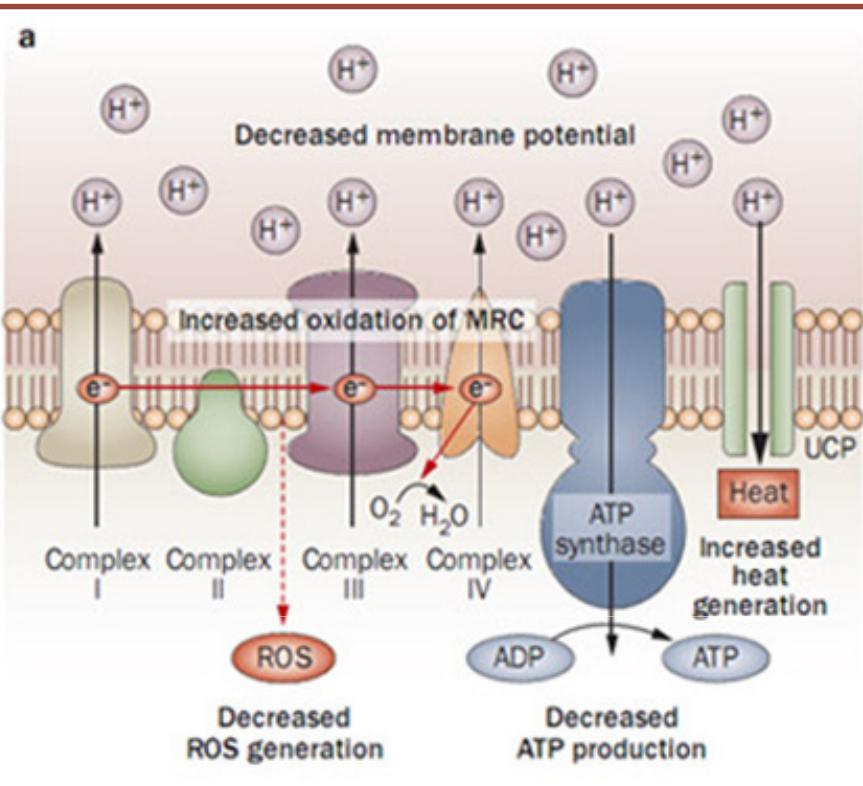
Baja Producción de Energia (ATP)  
Alta Producción de Calor  
Cluster mitocondrial JT

## Zonas Cálidas



Alta Producción de Energia (ATP)  
Baja Producción de Calor  
Cluster mitocondrial HV y haplogrupos Africanos

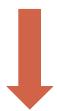
Condiciona nuestra salud hoy en día



### Uncoupled OXPHOS (mtDNA haplogroups T/J)

+

Nuclear background and environmental conditions



Decreased risk of OA  
severity and progression

### Coupled OXHPOS (mtDNA haplogroup H)

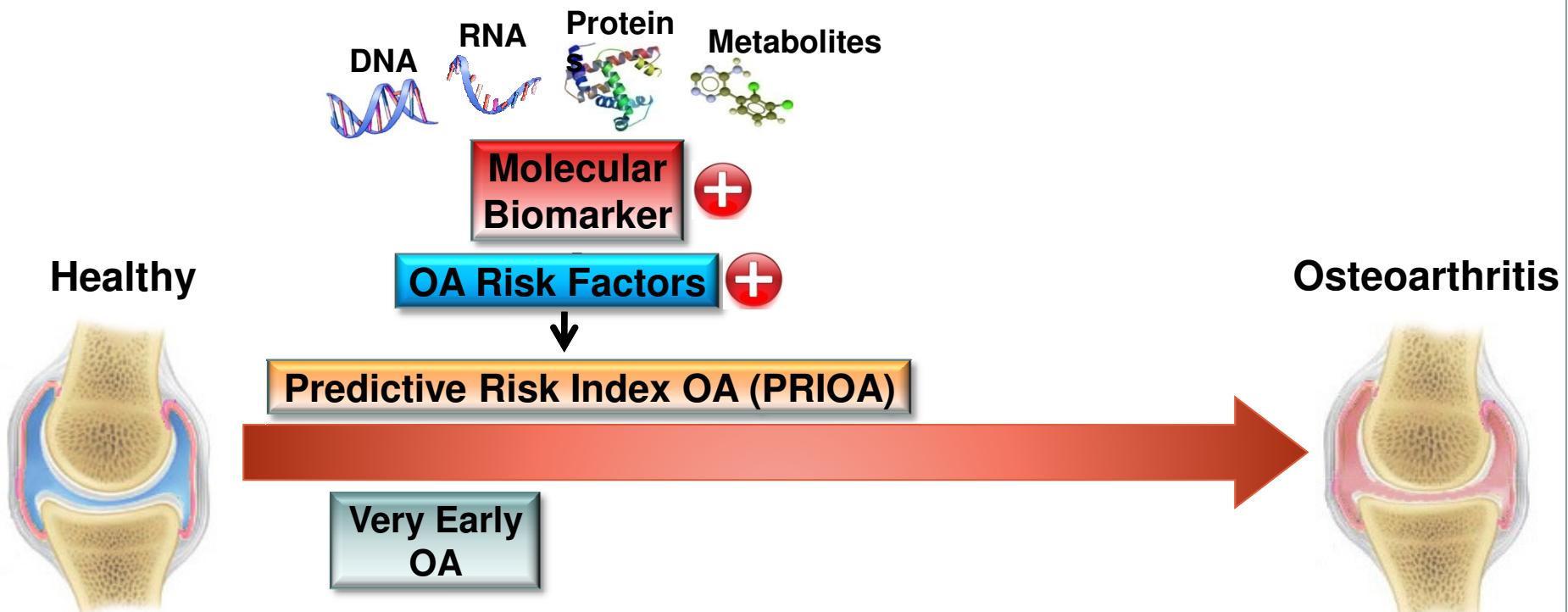
+

Nuclear background and environmental conditions



Increased risk of OA  
severity and progression

# LOS HAPLOGRUPOS MITOCONDRIALES COMO BIOMARCADORES DE ARTROSIS



## HAPLOGRUPOS COMO BIOMARCADORES DE ARTROSIS

- Biomarcadores genéticos diagnóstico
- Biomarcadores genéticos de severidad
- Biomarcadores genéticos complementarios
- Biomarcadores genéticos de progresión

# HAPLOGRUPOS COMO BIOMARCADORES DIAGNÓSTICO

**Table 2.** Frequencies and ORs of mtDNA haplogroups and SNPs in patients with knee OA\*

Haplogroup	No. (%) of control subjects (n = 262)	No. (%) of patients with knee OA (n = 457)	Total (n = 719)	OR (95% CI)	P
H	103 (39.3)	205 (44.9)	308 (42.8)	1.256 (0.922–1.710)	0.159
I	0 (0)	3 (0.7)	3 (0.4)	3.463 (0.317–37.788)	0.557
J	39 (14.9)	34 (7.4)	73 (10.2)	0.460 (0.282–0.748)	0.002†
K	20 (7.6)	39 (8.5)	59 (8.2)	1.129 (0.644–1.980)	0.778
T	23 (8.8)	34 (7.4)	57 (7.9)	0.835 (0.481–1.451)	0.567
U	48 (18.3)	69 (15.1)	117 (16.3)	0.793 (0.529–1.188)	0.294
V	8 (3.1)	17 (3.7)	25 (3.5)	1.227 (0.522–2.883)	0.833
SuperHV	5 (1.9)	16 (3.5)	21 (2.9)	1.865 (0.675–5.150)	0.258
W	0 (0)	3 (0.7)	3 (0.4)	3.463 (0.317–37.788)	0.557
X	4 (1.5)	14 (3.1)	18 (2.5)	2.038 (0.664–6.258)	0.321
Cluster HV	116 (44.3)	238 (52.1)	354 (49.2)	1.368 (1.008–1.856)	0.053
Cluster IWX	4 (1.5)	20 (4.4)	24 (3.3)	2.952 (0.998–8.732)	0.051
Cluster TJ	62 (23.7)	68 (14.9)	130 (18.1)	0.564 (0.384–0.828)	0.005†
Cluster KU	68 (26.0)	108 (23.6)	176 (24.5)	0.883 (0.622–1.253)	0.528
Others	12 (4.6)	23 (5.0)	35 (4.9)	1.104 (0.540–2.257)	0.859
SNPs					
T7028C	103 (39.0)	205 (44.9)	308 (42.7)	1.272 (0.935–1.730)	0.138
T14766C	116 (43.9)	242 (53.0)	358 (49.7)	1.436 (1.060–1.946)	0.021†
A10398G	68 (25.8)	89 (19.5)	157 (21.8)	0.697 (0.486–0.999)	0.061
G4580A	8 (3.0)	17 (3.7)	25 (3.5)	1.232 (0.536–2.828)	0.679
A12308G	68 (25.8)	108 (23.6)	176 (24.4)	0.892 (0.628–1.266)	0.530
T4216C	62 (23.5)	68 (14.9)	130 (18.0)	0.570 (0.388–0.836)	0.005†
T14798C	41 (15.6)	58 (12.7)	99 (13.8)	0.784 (0.509–1.207)	0.311
G15257A	10 (3.8)	16 (3.5)	26 (3.6)	0.914 (0.409–2.045)	0.838

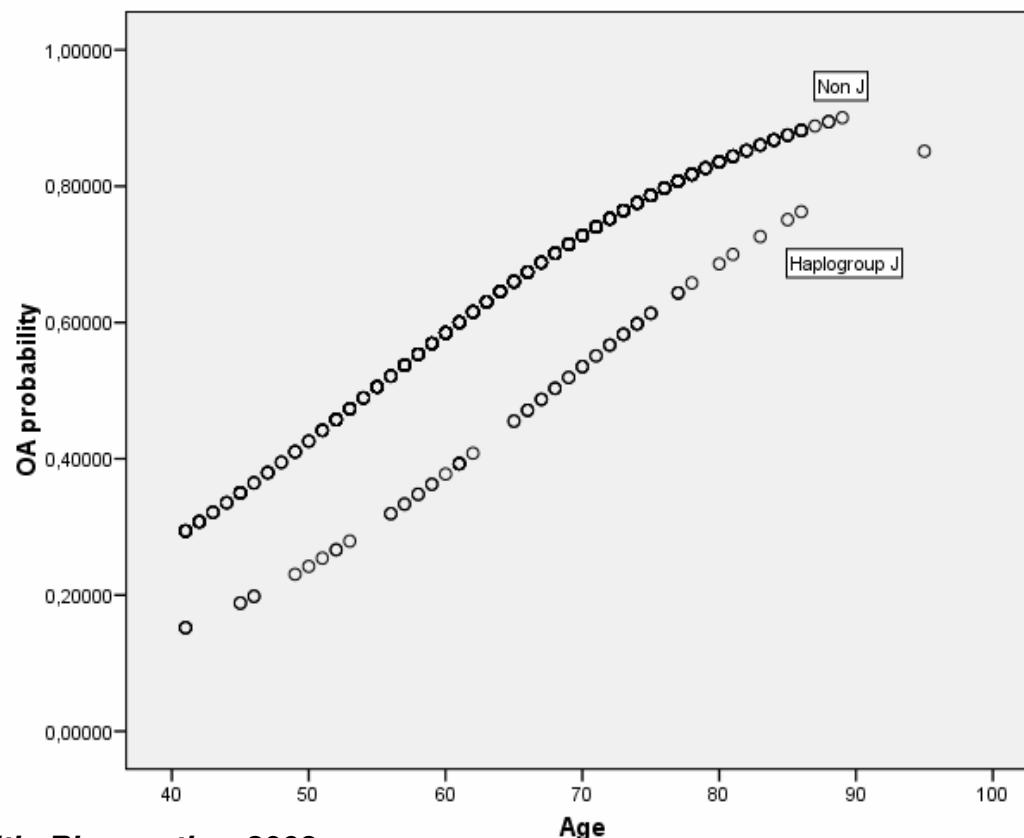
\* ORs = odds ratios; mtDNA = mitochondrial DNA; SNPs = single-nucleotide polymorphisms; OA = osteoarthritis; 95% CI = 95% confidence interval.

† Statistically significant ( $P < 0.05$ ).

Rego-Pérez et al. *Arthritis Rheumatism* 2008

# HAPLOGRUPOS COMO BIOMARCADORES DIAGNÓSTICO

El haplogrupo mitocondrial J se asocia con un menor riesgo de desarrollar Artrosis de rodilla en la población Gallega



Rego-Pérez et al. *Arthritis Rheumatism* 2008

# HAPLOGRUPOS COMO BIOMARCADORES DIAGNÓSTICO

El haplogrupo mitocondrial J se asocia con un menor riesgo de desarrollar  
Artrosis de cadera en la población Gallega

**Table 2** Frequencies and odds ratios (ORs) of mitochondrial DNA (mtDNA) haplogroups in subjects with hip osteoarthritis (OA)

Haplogroups	Control (n = 505)	Hip OA (n = 550)	Total (n = 1055)	OR	95% CI		p Value
					Lower CI	Upper CI	
H	225 (44.6)	251 (45.6)	476 (45.1)	1.045	0.819	1.332	0.724
I	3 (0.6)	3 (0.5)	6 (0.6)	0.918	0.184	4.568	1.000
J	60 (11.9)	45 (8.2)	105 (10)	0.661	0.440	0.993	0.045*
J <sub>1c</sub>	36 (7.2)	20 (3.7)	56 (5.3)	0.492	0.281	0.862	0.012*
J <sub>2</sub>	15 (3.0)	16 (2.9)	31 (3.0)	0.980	0.480	2.004	0.956
K	39 (7.7)	44 (8.0)	83 (7.9)	1.039	0.663	1.628	0.867
T	41 (8.1)	48 (8.7)	89 (8.4)	1.082	0.700	1.673	0.722
U	78 (15.4)	84 (15.3)	162 (15.4)	0.987	0.706	1.379	0.938
V	16 (3.2)	22 (4.0)	38 (3.6)	1.273	0.661	2.453	0.469
HV*	9 (1.8)	8 (1.5)	17 (1.6)	0.813	0.311	2.125	0.673
W	4 (0.8)	1 (0.2)	5 (0.5)	0.228	0.025	2.048	0.200
X	14 (2.8)	10 (1.8)	24 (2.3)	0.649	0.286	1.476	0.299
Others	16 (3.2)	34 (6.2)	50 (4.7)	2.014	1.098	3.695	0.021*

Values shown are number (%) of subjects. SNP frequencies refer to the minor alleles.

\*p<0.05.

Rego et al. *Ann Rheum Dis* 2009

# HAPLOGRUPOS COMO BIOMARCADORES DIAGNÓSTICO



Contents lists available at ScienceDirect

## Mitochondrion

journal homepage: [www.elsevier.com/locate/mito](http://www.elsevier.com/locate/mito)



## mtDNA haplogroups and osteoarthritis in different geographic populations



A. Soto-Hermida <sup>a,c</sup>, M. Fernández-Moreno <sup>a,c</sup>, N. Oreiro <sup>a,c</sup>, C. Fernández-López <sup>a,c</sup>,  
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# HAPLOGRUPOS COMO BIOMARCADORES DIAGNÓSTICO

El haplogrupo mitocondrial T se asocia con un menor riesgo de desarrollar Artrosis de rodilla en la población Inglesa

**Table 3**

Logistic regression analysis in OA patients and healthy controls from Spain and UK.

Variables	B	OR	95% CI	p <sup>a</sup>
<i>Spanish cohort</i>				
Gender (male)	-0.344	0.709	0.568–0.884	0.002*
Age (years)	0.032	1.032	1.023–1.041	<0.001*
Haplogroup J	-0.453	0.636	0.444–0.911	0.013*
<i>UK cohort</i>				
Gender (male)	-1.200	0.301	0.218–0.416	<0.001*
Age (years)	0.050	1.051	1.027–1.075	<0.001*
Haplogroup T	-0.556	0.574	0.350–0.939	0.027*

B = regression coefficient.

OR = odds ratio.

CI = confidence interval.

<sup>a</sup> p-Value from the logistic regression analysis.

\* Statistical significance at  $p \leq 0.05$ .

Soto-Hermida et al. *Mitochondrion* 2014

# HAPLOGRUPOS COMO BIOMARCADORES DIAGNÓSTICO

*Int. J. Mol. Sci.* **2014**, *15*, 2646–2659; doi:10.3390/ijms15022646

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Article

## Role of mtDNA Haplogroups in the Prevalence of Knee Osteoarthritis in a Southern Chinese Population

Hezhi Fang <sup>1,†</sup>, Xinwei Liu <sup>2,†</sup>, Lijun Shen <sup>1,†</sup>, Fengjie Li <sup>1</sup>, Yihong Liu <sup>1</sup>, Hongbo Chi <sup>1</sup>,  
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**Table 2.** Effect of mitochondrial DNA haplogroup in patients with knee OA.

Haplogroup	Patient (n = 187)	Control (n = 420)	OR (95% CI)	p value
<b>M</b>	103 (55.1)	211 (50.2)	1.215 (0.859, 1.716)	0.270
<b>D</b>	40 (21.2)	90 (21.4)	0.998 (0.655, 1.519)	0.992
<b>D4</b>	17 (9.1)	57 (13.6)	0.637 (0.360, 1.128)	0.119
<b>D4a</b>	4 (2.1)	18 (4.3)	0.488 (0.163, 1.463)	0.191
<b>D5</b>	21 (11.2)	31 (7.4)	1.587 (0.886, 2.844)	0.118
<b>D5a</b>	5 (2.7)	8 (1.9)	1.415 (0.457, 4.383)	0.546
<b>M8</b>	21 (11.2)	39 (9.3)	1.415 (0.457, 4.383)	0.546
<b>M8a</b>	7 (3.7)	10 (2.38)	1.594 (0.597, 4.2550)	0.348
<b>CZ</b>	14 (7.5)	28 (6.67)	1.136 (0.584, 2.211)	0.708
<b>M7</b>	8 (4.3)	32 (7.6)	0.542 (0.245, 1.2)	0.126
<b>M7b</b>	3 (1.6)	20 (4.8)	0.326 (0.096, 1.111)	0.06
<b>M7c</b>	4 (2.1)	8 (1.9)	1.114 (0.331, 3.744)	0.862
<b>G</b>	8 (4.3)	6 (1.4)	3.084 (1.055, 9.017)	0.031 *
<b>M9</b>	4 (2.1)	4 (1.0)	1.180 (0.291, 4.7860)	0.819
<b>M10</b>	5 (2.6)	8 (1.9)	1.415 (0.457, 4.384)	0.546
<b>N</b>	84 (44.9)	209 (49.8)	1.215 (0.859, 1.716)	0.270
<b>A</b>	18 (9.6)	35 (8.33)	1.171 (0.645, 2.127)	0.603
<b>N9</b>	12 (6.4)	20 (4.8)	1.548 (0.739, 3.243)	0.243
<b>N9a</b>	9 (4.8)	14 (3.3)	1.475 (0.627, 3.470)	0.371
<b>Y</b>	3 (1.6)	6 (1.4)	1.125 (0.278, 4.5470)	0.869
<b>R</b>	54 (28.9)	156 (37.1)	0.687 (0.473, 0.998)	0.048 *
<b>R11</b>	4 (2.1)	5 (1.2)	1.814 (0.482, 6.834)	0.372
<b>B</b>	19 (10.1)	74 (17.6)	0.529 (0.309, 0.904)	0.018 *
<b>B4</b>	13 (7.0)	52 (12.4)	0.529 (0.280, 0.997)	0.046 *
<b>B5</b>	6 (3.2)	19 (4.5)	0.717 (0.282, 1.8250)	0.484
<b>R9</b>	27 (14.4)	71 (16.9)	0.829 (0.513, 1.342)	0.446
<b>F</b>	21 (11.2)	62 (14.8)	0.730 (0.431, 1.239)	0.242
<b>F1</b>	13 (7.0)	38 (9.0)	0.751 (0.390, 1.446)	0.390
<b>F1a</b>	4 (2.1)	25 (6.0)	0.350 (0.12, 1.0)	0.045 *
<b>F1b</b>	6 (3.2)	8 (1.9)	1.707 (0.584, 4.991)	0.323
<b>F2</b>	8 (4.2)	17 (4.0)	1.059 (0.449, 2.500)	0.895
<b>F2a</b>	4 (2.1)	7 (1.67)	1.290 (0.373, 4.460)	0.687

p values were estimated by “chi-square test”; (\*) indicated statistical significant ( $p < 0.05$ ); OR indicates odds ratio; 95% CI, 95% confidence interval; values in ( ) are the percentage (%) of samples.

# HAPLOGRUPOS COMO BIOMARCADORES DE SEVERIDAD

## El haplogrupo mitocondrial J se asocia con una menor severidad radiológica de Artrosis de rodilla

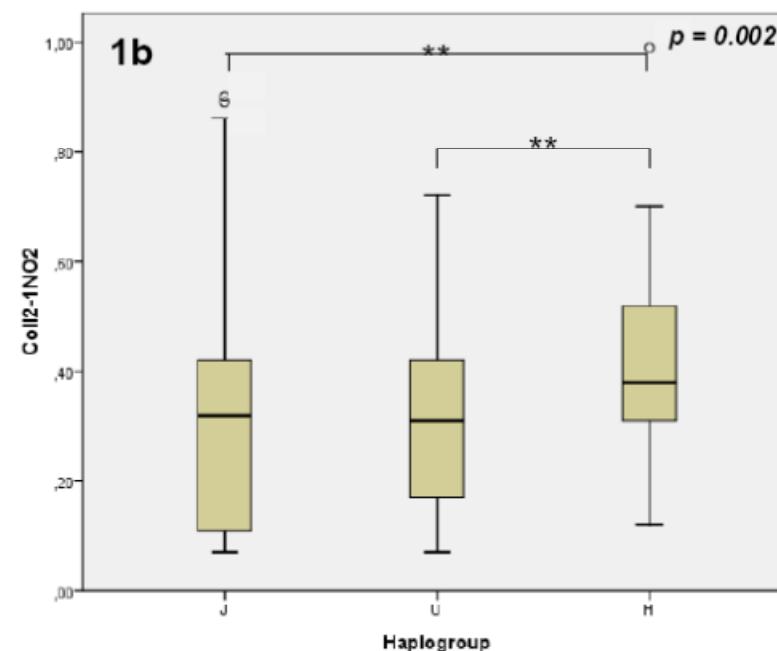
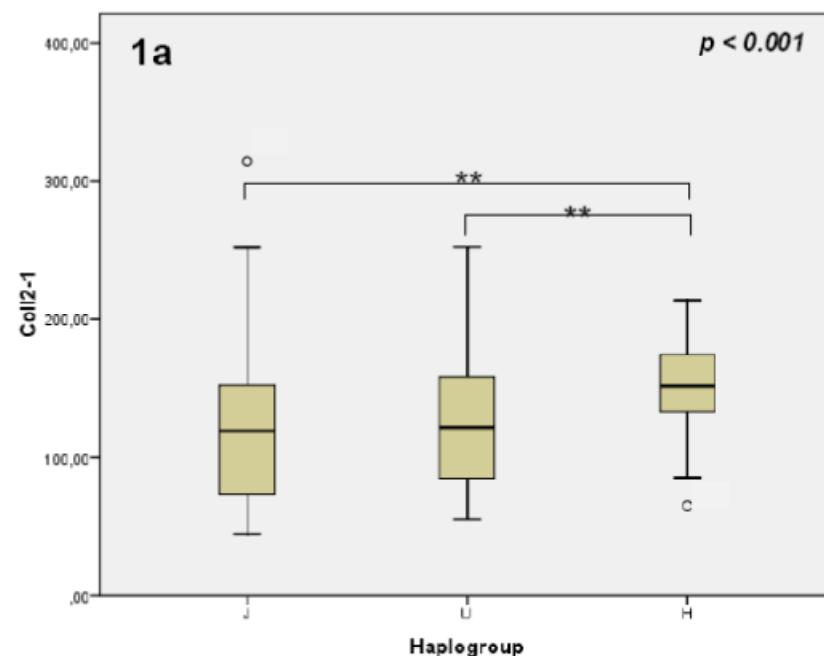
**Table 4.** Frequencies and ORs of mtDNA haplogroups and SNPs in OA patients, by K/L grade of knee OA\*

Haplogroup	K/L grades 1–3 (n = 337)	K/L grade 4 or prosthesis (n = 164)	Total (n = 501)	OR (95% CI)	P
H	146 (43.3)	76 (46.3)	222 (44.3)	1.130 (0.778–1.641)	0.566
I	2 (0.6)	1 (0.6)	3 (0.6)	1.028 (0.134–7.900)	1.000
J	38 (11.3)	7 (4.3)	45 (9.0)	0.351 (0.156–0.787)	0.012†
K	27 (8.0)	15 (9.1)	42 (8.4)	1.156 (0.603–2.215)	0.732
T	22 (6.5)	13 (7.9)	35 (7.0)	1.233 (0.612–2.481)	0.578
U	43 (12.8)	34 (20.7)	77 (15.4)	1.788 (1.094–2.922)	0.025†
V	14 (4.2)	4 (2.4)	18 (3.6)	0.577 (0.197–1.692)	0.446
SuperHV	13 (3.9)	4 (2.4)	17 (3.4)	0.623 (0.211–1.843)	0.600
W	2 (0.6)	1 (0.6)	3 (0.6)	1.028 (0.134–7.900)	1.000
X	12 (3.6)	2 (1.2)	14 (2.8)	0.334 (0.083–1.349)	0.160
Cluster HV	173 (51.3)	84 (51.2)	257 (51.3)	0.995 (0.686–1.444)	1.000
Cluster IWX	16 (4.7)	4 (2.4)	20 (4.0)	0.502 (0.173–1.452)	0.330
Cluster TJ	60 (17.8)	20 (12.2)	80 (16.0)	0.641 (0.374–1.099)	0.120
Cluster KU	70 (20.8)	49 (29.9)	119 (23.8)	1.625 (1.064–2.481)	0.033†
Others	18 (5.3)	7 (4.3)	25 (5.0)	0.790 (0.332–1.882)	0.669
SNPs					
T7028C	146 (43.3)	76 (46.3)	222 (44.3)	1.130 (0.777–1.644)	0.566
T14766C	175 (51.9)	86 (52.4)	261 (52.1)	1.021 (0.702–1.483)	0.924
A10398G	78 (23.1)	27 (16.5)	105 (21.0)	0.654 (0.405–1.058)	0.101
G4580A	14 (4.2)	4 (2.4)	18 (3.6)	0.577 (0.187–1.781)	0.446
A12308G	70 (20.8)	49 (29.9)	119 (23.8)	1.625 (1.064–2.481)	0.033†
T4216C	60 (17.8)	20 (12.2)	80 (16.0)	0.641 (0.374–1.099)	0.120
T14798C	49 (14.5)	19 (11.6)	68 (13.6)	0.770 (0.440–1.348)	0.406
G15257A	14 (4.2)	5 (3.0)	19 (3.8)	0.726 (0.267–1.969)	0.626

Rego-Pérez et al. *Arthritis Rheumatism* 2008

## HAPLOGRUPOS COMO BIOMARCADORES COMPLEMENTARIOS

**Los haplogrupos mitocondriales modulan los niveles séricos de biomarcadores de colágeno tipo II**



N = 150 muestras (75 OA and 75 sanos)

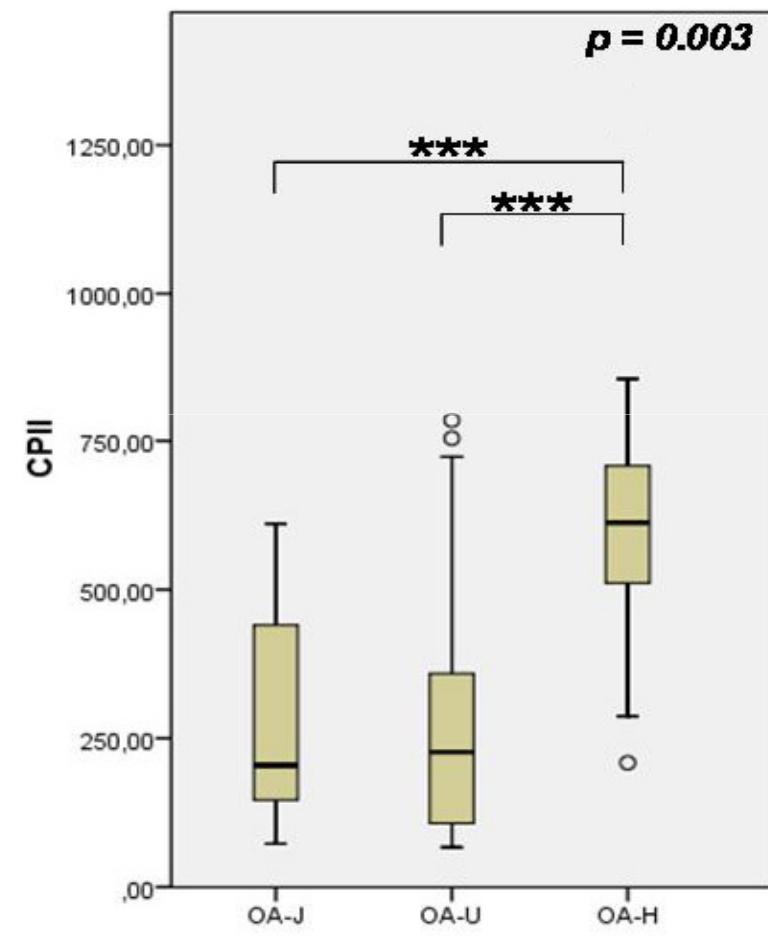
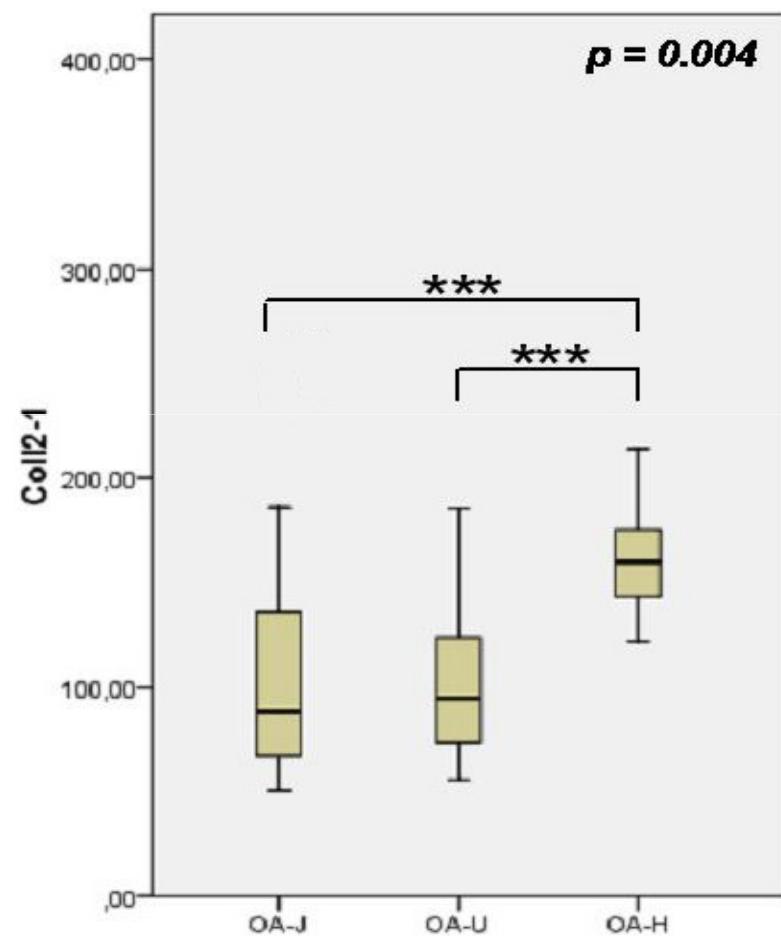
Rego-Pérez et al. *Ann Rheum Dis* 2010

Ignacio Rego-Pérez

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SOANRE 2014

## HAPLOGRUPOS COMO BIOMARCADORES COMPLEMENTARIOS



Rego-Pérez et al. *Ann Rheum Dis* 2010

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# HAPLOGRUPOS COMO BIOMARCADORES COMPLEMENTARIOS

## Los haplogrupos mitocondriales definen fenotipos diferentes de Artrosis

Table 3 | Multivariate logistic regression analysis for diagnosis of osteoarthritis (OA) in haplogroup H and J carriers.

Variables	B	OR	95% CI	p*
<b>HAPLOGROUP H</b>				
Age	0.263	1.301	1.026–1.649	0.030**
BMI	0.647	1.910	1.124–3.244	0.017**
MMP-13	0.430	1.537	1.023–2.310	0.038**
Coll2-1	0.104	1.110	1.013–1.217	0.026**
<b>HAPLOGROUP J</b>				
BMI	0.404	1.499	1.062–2.115	0.021**
Gender	-1.930	0.145	0.026–0.816	0.028**
MMP-13	0.551	1.735	1.017–2.959	0.043**

B = regression coefficient.

OR, odd ratio.

CI, confidence interval.

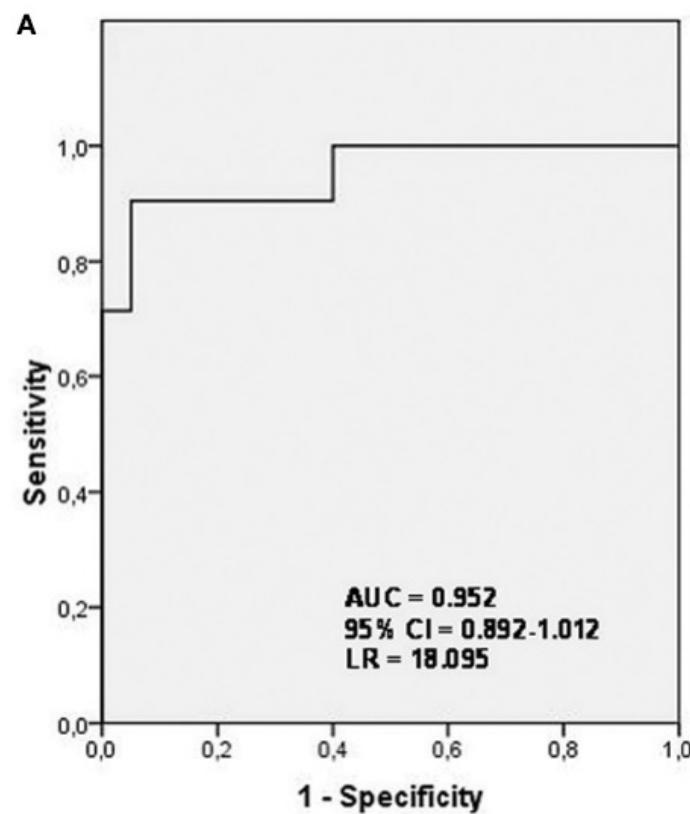
\*p-Value from the logistic regression model.

\*\*Statistical significance declared at p ≤ 0.05.

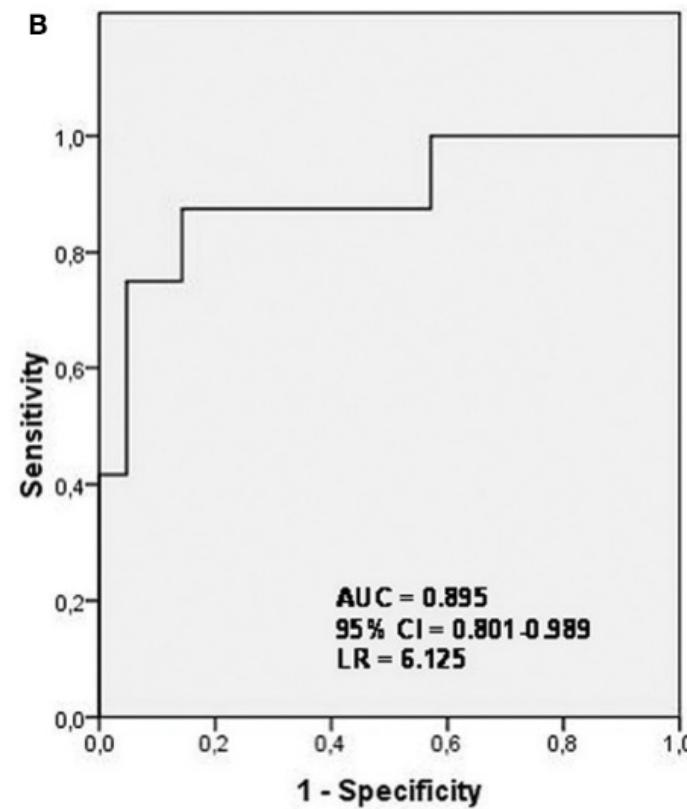
Fernández-Moreno et al. *Frontiers in Physiol* 2012

# HAPLOGRUPOS COMO BIOMARCADORES COMPLEMENTARIOS

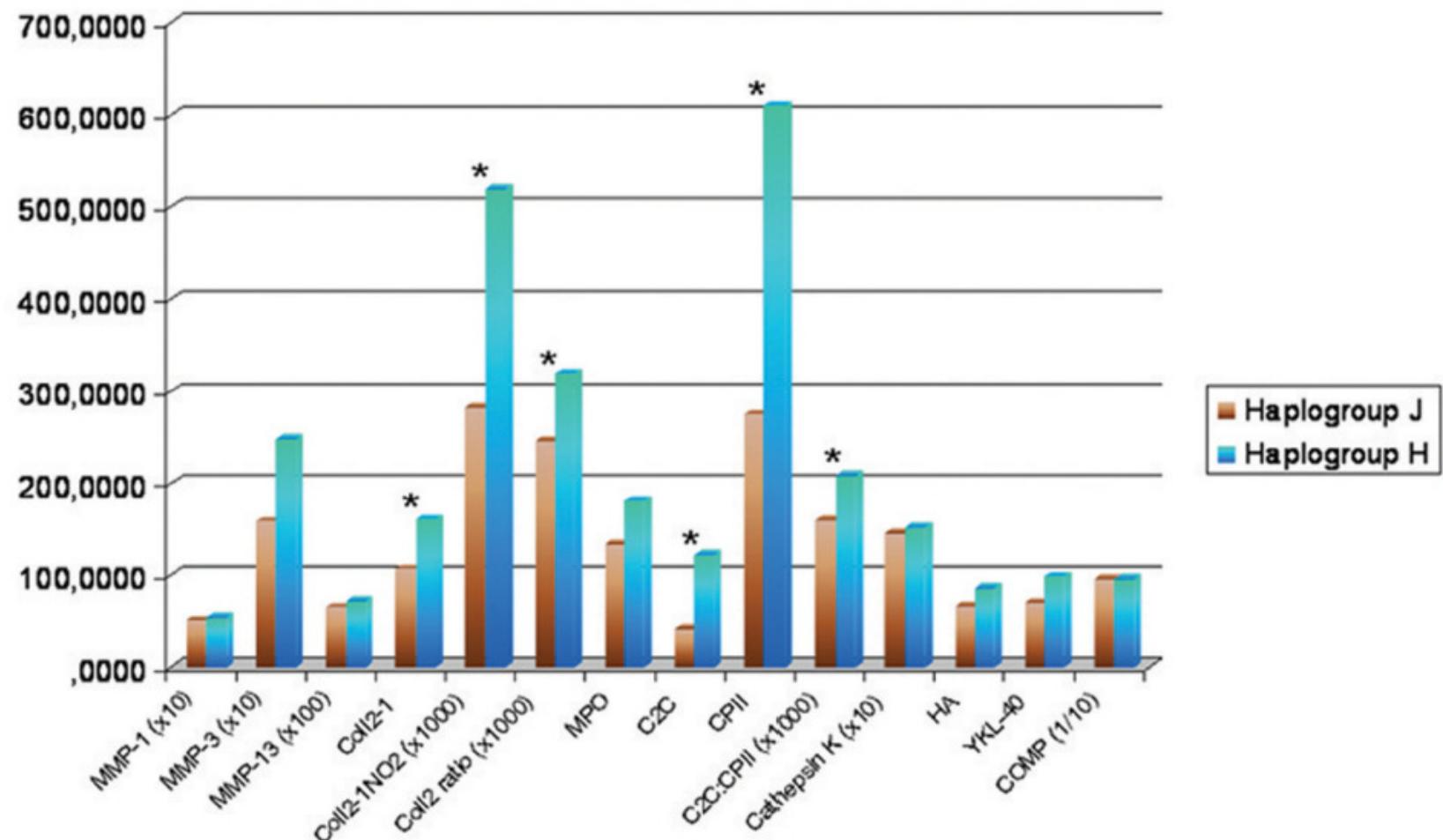
Haplogrupo H



Haplogrupo J



## HAPLOGRUPOS COMO BIOMARCADORES COMPLEMENTARIOS



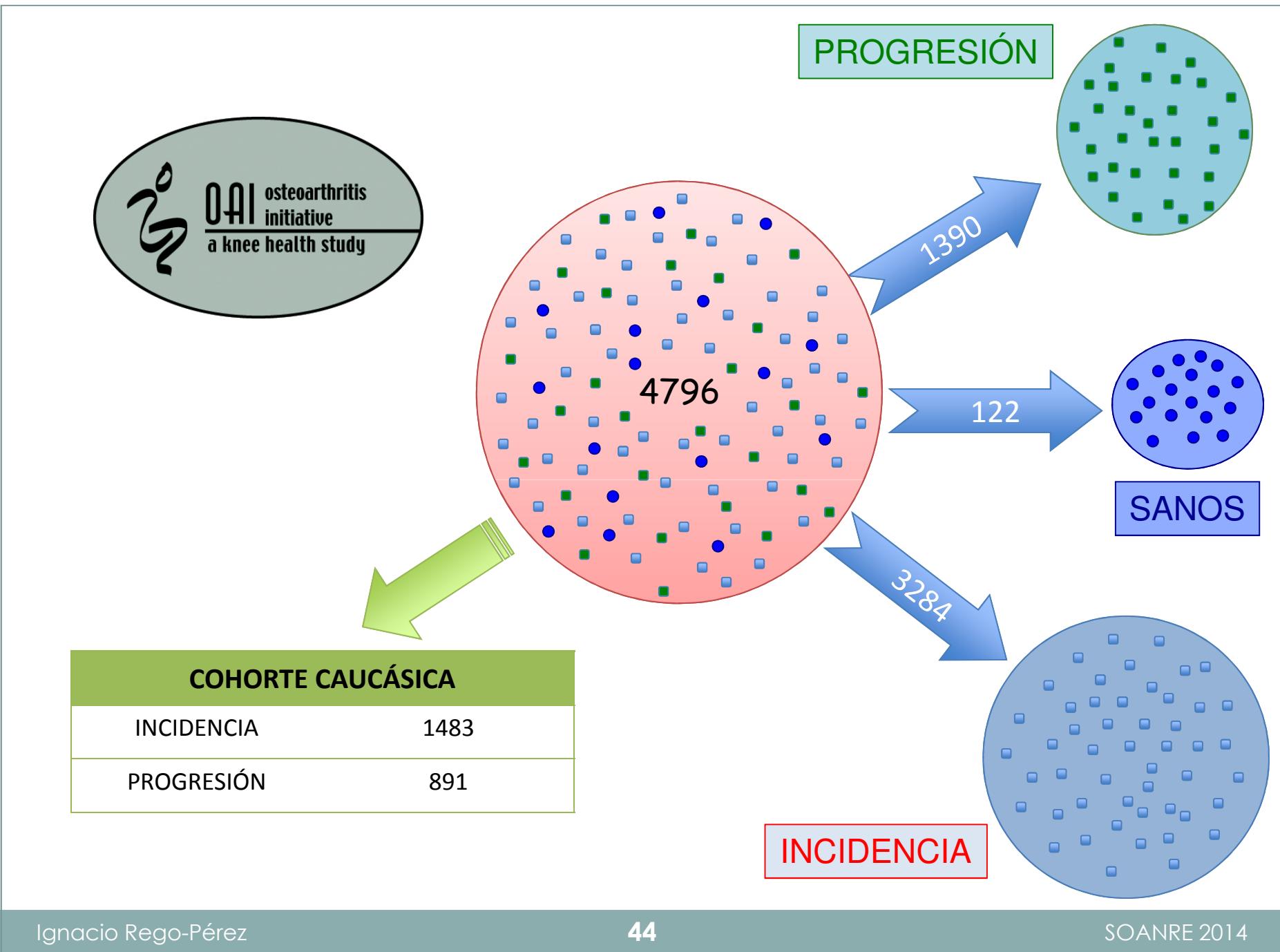
Fernández-Moreno et al. *Frontiers in Physiol* 2012

## HAPLOGRUPOS COMO BIOMARCADORES DE PROGRESIÓN

- Cohorte de seguimiento Americana del OAI (Osteoarthritis Initiative)
- Cohorte Gallega PROCOAC (PROspective Cohort of OA from Coruña)

# COHORTE DEL OAI





# Radiographic OA progression

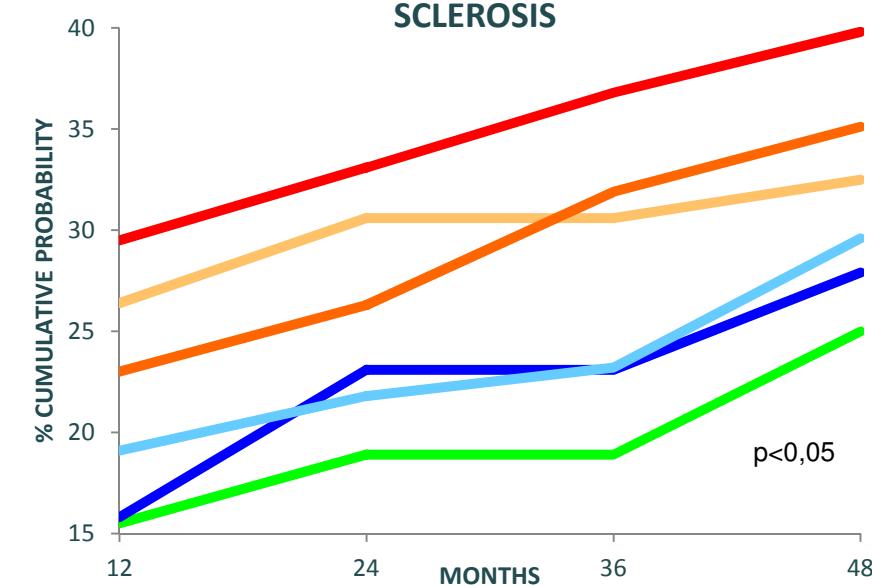
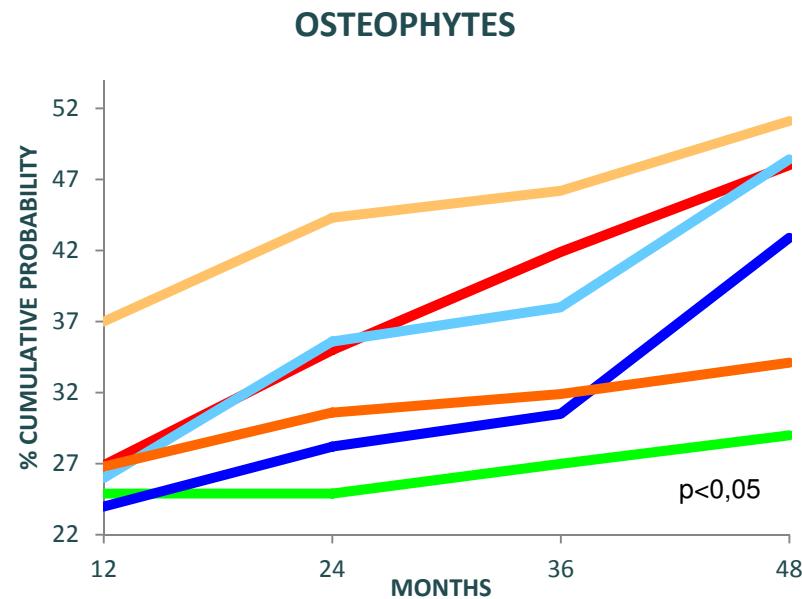
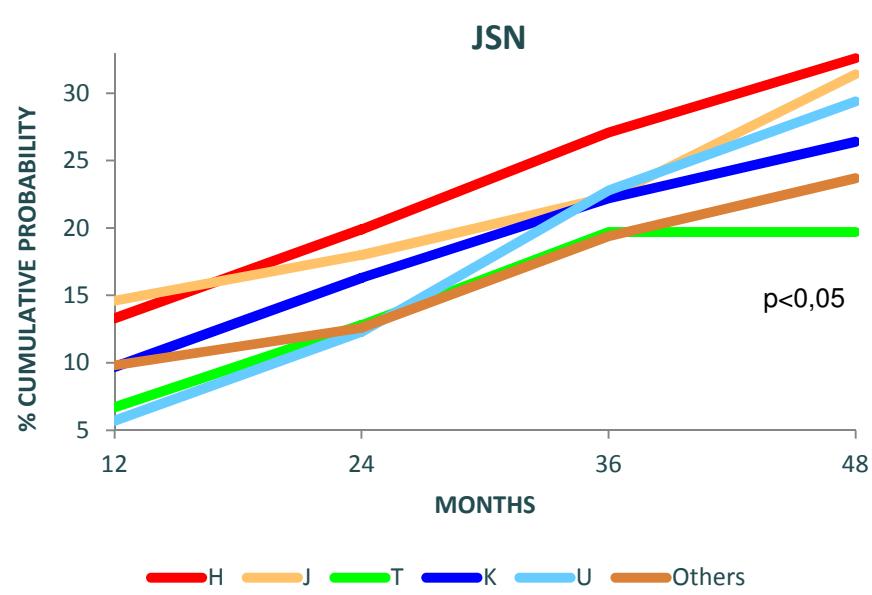
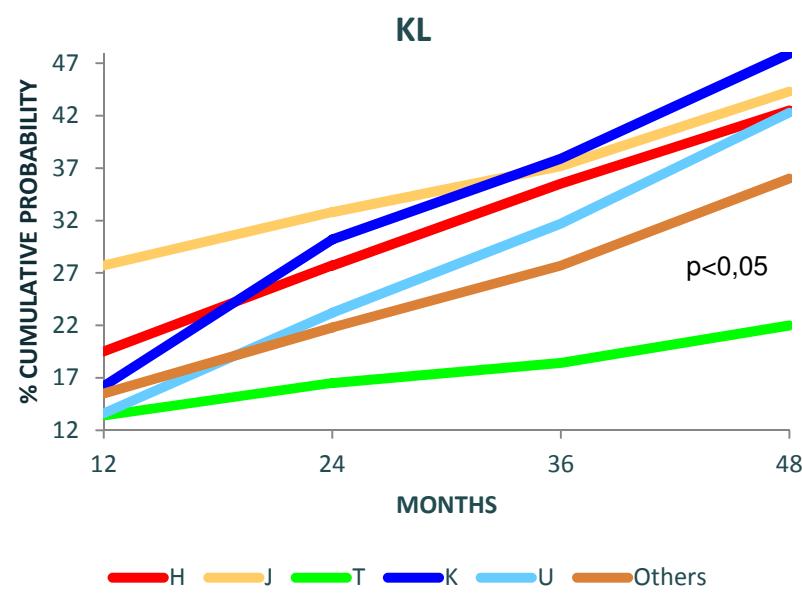
## Study cohort

Individuals with Caucasian ancestry of the OAI cohort

- ✓ Progression subcohort: **891** OA patients
- ✓ Follow-up period: **48** months

Variable	Progression criteria
KL Grade	Increase of at least one KL grade at any knee
Osteophytes	Increase of at least one OARSI atlas grade at any knee
Sclerosis	Increase of at least one OARSI atlas grade at any knee
JSN	Increase in score by a grade of $\geq 0.5$ at any knee
mJSW at $x=0.225$	Difference between baseline and 48 months in JSN and non-JSN knees

Soto-Hermida et al. *PLoS One* in press 2014

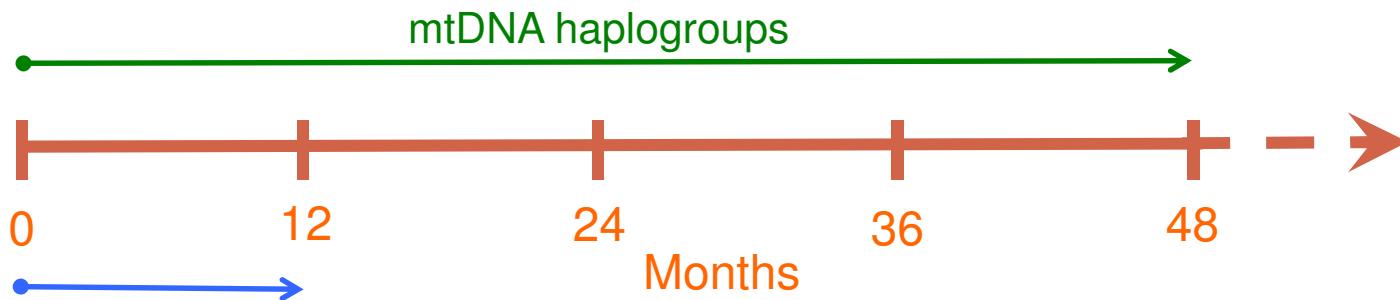


# Medial Joint Space Width (mJSW)

*Arthritis Care Res (Hoboken). 2010 July ; 62(7): 924–931. doi:10.1002/acr.20149.*

## One-Year Change in Radiographic Joint Space Width in Patients With Unilateral Joint Space Narrowing: Data From The Osteoarthritis Initiative

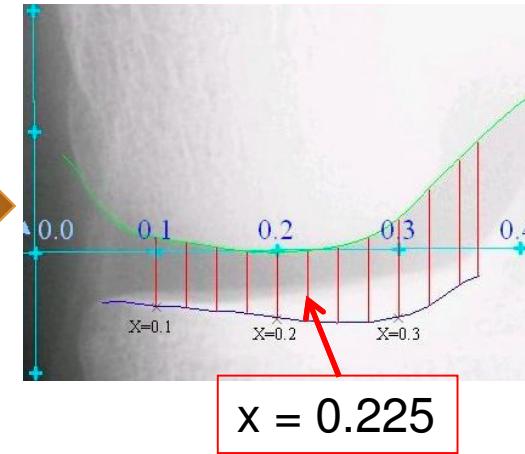
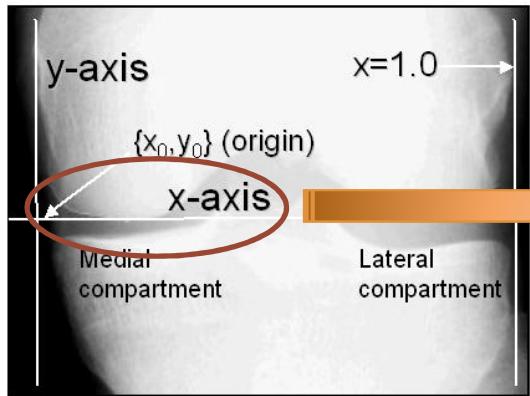
O. D. BENICHOU, MD, PhD<sup>1</sup>, D. J. HUNTER, MBBS, PhD, FRACP<sup>2</sup>, D. R. NELSON, MS<sup>1</sup>, A. GUERMAZI, MD<sup>3</sup>, F. ECKSTEIN, MD<sup>4</sup>, K. KWOKH, MD<sup>5</sup>, S. L. MYERS, MD<sup>1</sup>, W. WIRTH, MS<sup>4</sup>, and J. DURYEA, PhD<sup>6</sup> for the OSTEOARTHRITIS INITIATIVE INVESTIGATORS



### Inclusion criteria

Patients with unilateral medial JSON at baseline (N=249)

# Medial Joint Space Width (mJSW)



Difference in mJSW at  $x=0.225$   
between baseline and visit 6 (48  
months) for **JSN knees**

Difference in mJSW at  $x=0.225$   
between baseline and visit 6 (48  
months) for **non JSN knees**

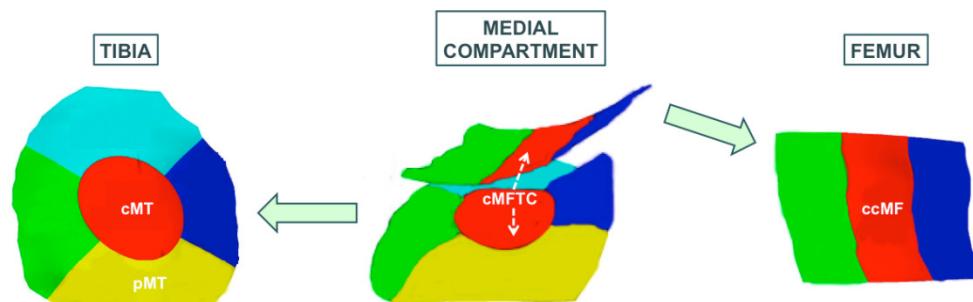
Haplogroup (N)	Mean $\pm$ SD	
N=249		
H (99)	0,5587 $\pm$ 0,7361	
J (29)	0,6697 $\pm$ 0,7245	
T (25)	<b>0,4924 <math>\pm</math> 0,5980</b>	
K (15)	0,538 $\pm$ 0,4391	
U (40)	0,6327 $\pm$ 0,9615	
Others (41)	0,6883 $\pm$ 0,7229	
<b>p-value</b>	N.S	<b>0,027*</b>

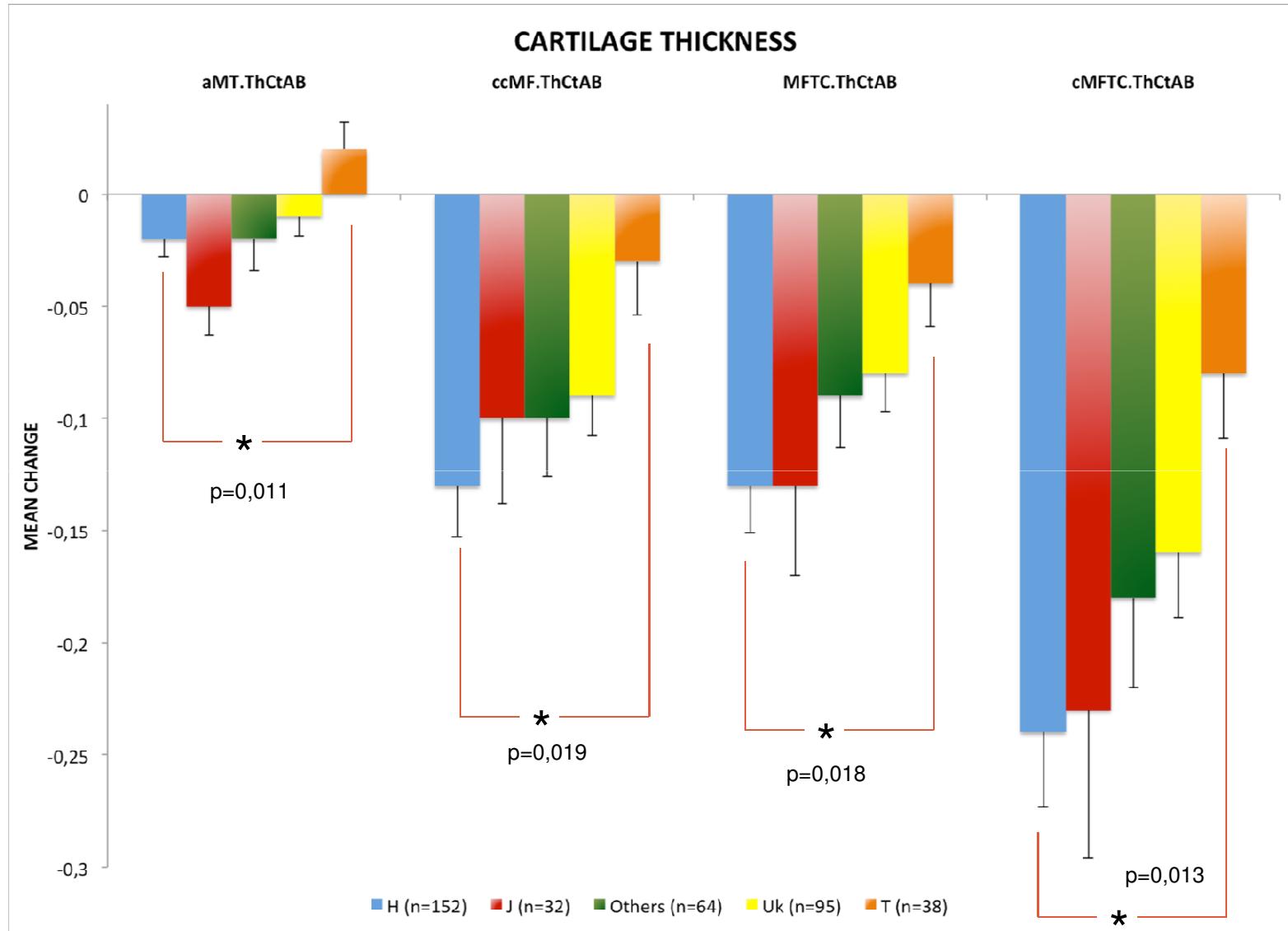
\* Multivariant analysis adjusting by age, gender and BMI at baseline; N.S: non significant; SD: standard deviation

# Resonancia magnética

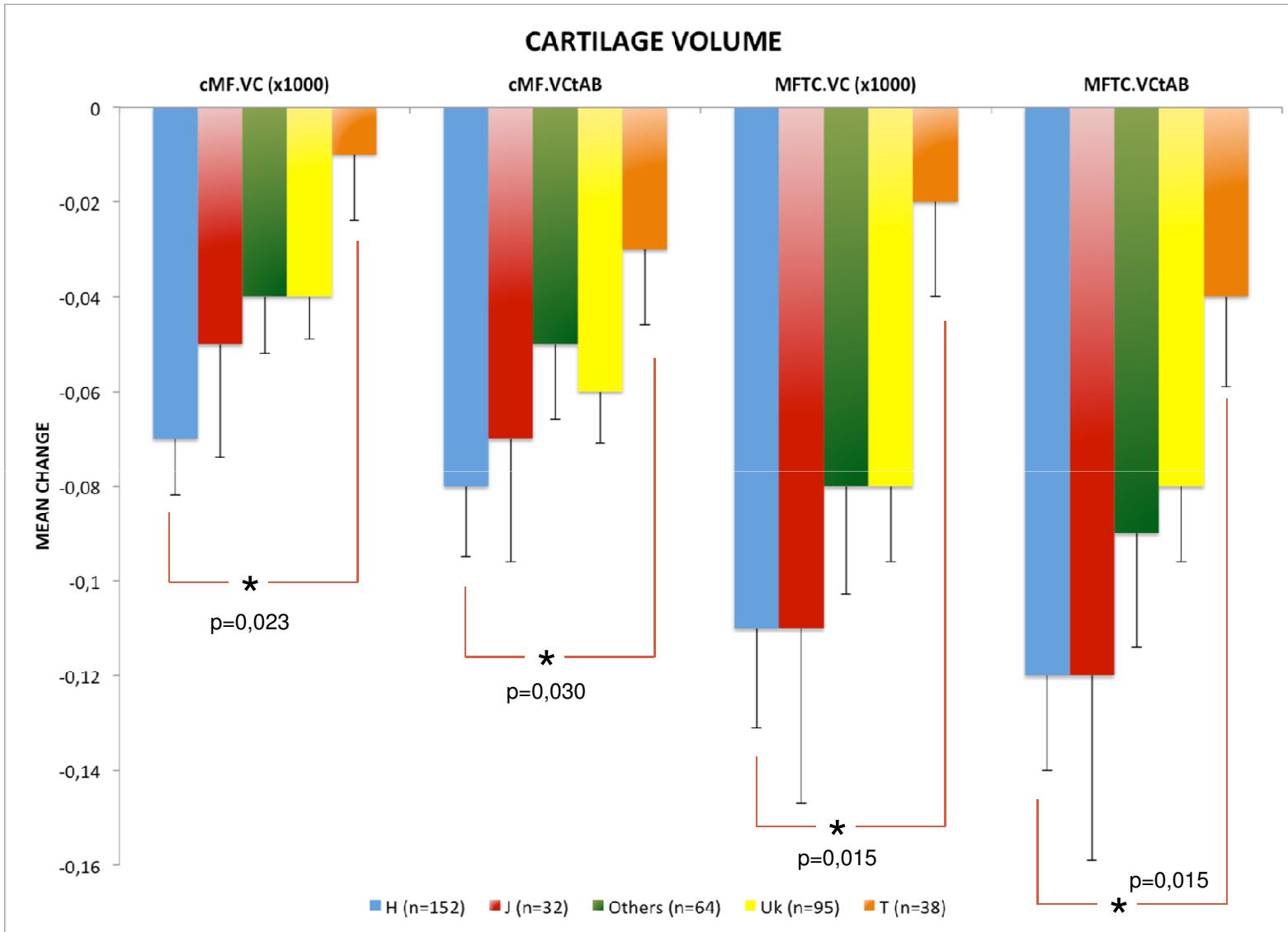
Medidas cuantitativas de morfología del cartílago (grosor y volumen en el compartimento medial) a partir de imágenes de Resonancia Magnética (Felix Eckstein: Chondrometrics -Germany- and Paracelsus -Austria-). Estudio prospectivo a 2 años

CLASSIFICATION OF SAMPLES ACCORDING TO PROJECTS			
PROYECTO	MUESTRAS	RODILLA	SAMPLES CHARACTERISTICS
9	381	Derecha e Izquierda	-Subcohorte de <b>Progresión</b> - <b>OA sintomática</b> en al menos una rodilla: osteofitos (grados 1-3) y síntomas frecuentes de OA en la misma rodilla. - <b>Grado KL 2 o 3.</b>





Soto-Hermida et al. *PLoS One* in press 2014



Soto-Hermida et al. *PLoS One* in press 2014

## COHORTE DEL OAI

### Study group (follow-up period: 4 years)

- ✓ **1537** OA patients with Caucasian ancestry from the Osteoarthritis Initiative (OAI) with KL grade = 0 - 1 at baseline in one or both knees, of which:
  - 214** patients developed incident knee OA during the follow-up period
  - 1323** patients remained stable during the follow-up period
- ✓ **837** OA patients with KL $\geq$ 2 at baseline in both knees (or missing data) were not considered

# COHORTE DEL OAI

Variables en la ecuación

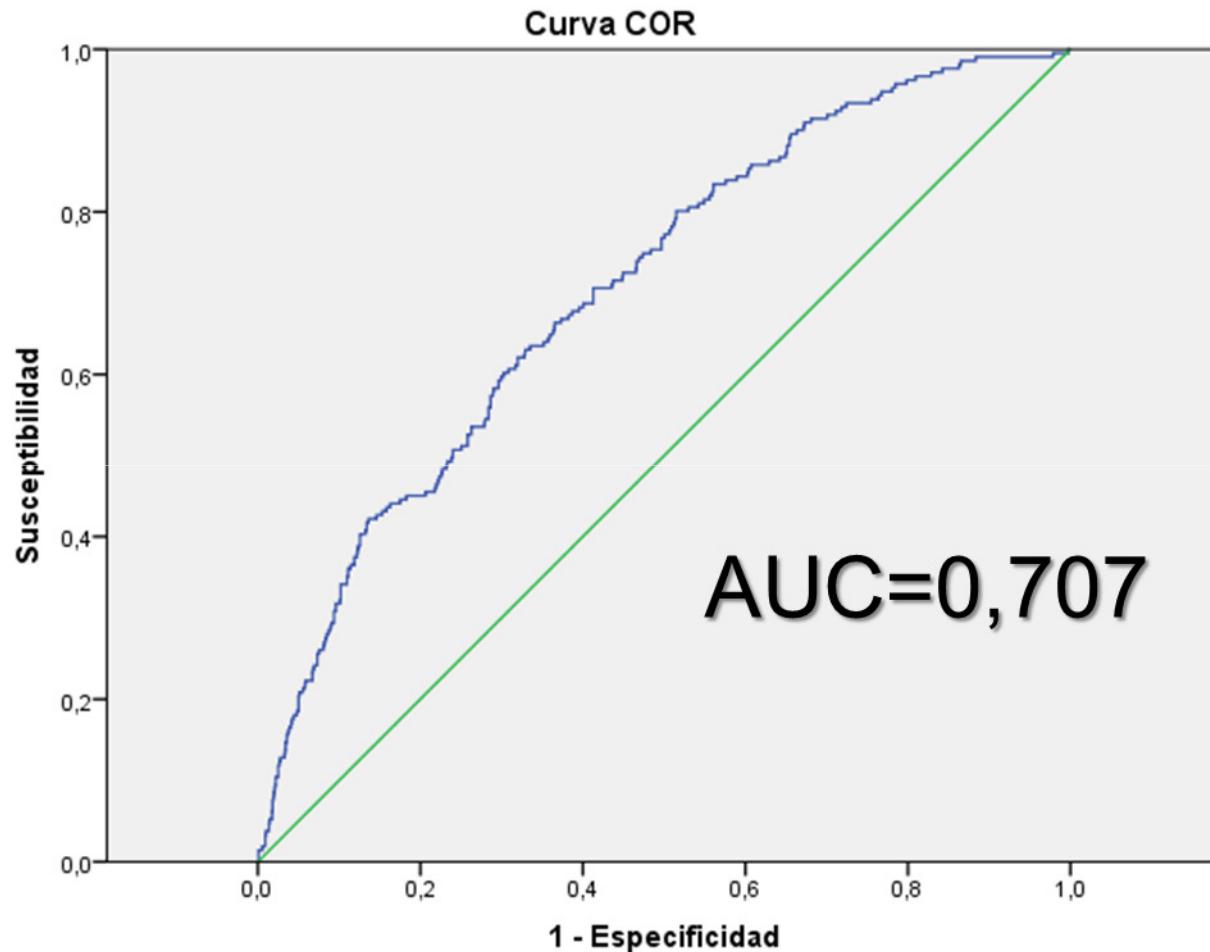
	B	E.T.	Wald	gl	Sig.	Exp(B)	I.C. 95% para EXP(B)	
							Inferior	Superior
Paso 1 <sup>a</sup>	P02SEX	,716	,165	18,809	1	,000	2,047	1,481 2,830
	V00AGE	,014	,009	2,661	1	,103	1,015	,997 1,032
	Cluster			9,387	3	,025		
	KU vs HV	-,153	,189	,651	1	,420	,858	,592 1,244
	TJ vs HV	-,550	,220	6,239	1	,012	,577	,375 ,888
	Others vs HV	-,669	,308	4,706	1	,030	,512	,280 ,937
	P01BMI	,049	,017	7,992	1	,005	1,050	1,015 1,086
	KOOSQOL.Mean	-,018	,004	17,745	1	,000	,982	,973 ,990
	ContralateralOA	,562	,163	11,816	1	,001	1,754	1,273 2,417
	V00BISPHOS	-,576	,270	4,570	1	,033	,562	,331 ,953
	V00PCTCARB	-,018	,008	4,670	1	,031	,982	,966 ,998
	V00DTVITD	-,002	,001	3,746	1	,053	,998	,997 1,000
	Constante	-2,886	,937	9,478	1	,002	,056	

a. Variable(s) introducida(s) en el paso 1: P02SEX, V00AGE, Cluster, P01BMI, KOOSQOL.Mean, ContralateralOA, V00BISPHOS, V00PCTCARB, V00DTVITD.

## Step-wise forward approach

*Unpublished data*

## COHORTE DEL OAI



*Unpublished data*

# COHORTE PROCOAC

Rheumatol Int  
DOI 10.1007/s00296-014-3104-1

ORIGINAL ARTICLE

## Mitochondrial DNA haplogroups modulate the radiographic progression of Spanish patients with osteoarthritis

Angel Soto-Hermida · Mercedes Fernández-Moreno · Sonia Pértega-Díaz ·  
Natividad Oreiro · Carlos Fernández-López · Francisco J. Blanco ·  
Ignacio Rego-Pérez

# Progresión radiológica

## Cohorte de estudio

Pacientes gallegos con artrosis

- ✓ Cohorte de progresión: 281 pacientes
- ✓ Período de seguimiento no inferior a 36 meses

Variable	Criterio de progresión
Grado KL	Incremento de, al menos, 1 grado KL durante el seguimiento
Prótesis	Pacientes que progresan a prótesis durante el período de seguimiento

Soto-Hermida et al. *Rheumatology Int* 2014

## COHORTE PROCOAC

### Progresión radiológica en base a incremento en el grado KL

**Table 2** Multivariate Cox regression analysis of radiographic osteoarthritis (OA) progression

*B* regression coefficient, *HR* hazard ratio, *CI* confidence interval, *BMI* body mass index

\* Statistical significance at  $p \leq 0.05$

# This group includes both minor European haplogroups *I*, *W*, *X* and non-European

<sup>c</sup> *p* value from the Cox regression model

Variables	<i>B</i>	HR	95 % CI	<i>p</i> <sup>c</sup>
Radiographic OA progression analyzed by mtDNA clusters				
Gender (male)	0.044	1.045	0.747–1.463	0.796
Age (years)	0.039	1.040	1.023–1.056	<0.001*
BMI ( $>30 \text{ kg/m}^2$ )	0.031	1.032	0.772–1.380	0.832
mtDNA clusters				0.134
HV versus TJ	0.230	1.258	0.794–1.993	0.328
KU versus TJ	0.537	1.711	1.037–2.823	0.036*
Others# versus TJ	0.181	1.199	0.678–2.118	0.533
Radiographic OA progression analyzed by carriers of mtDNA haplogroup H versus non-H				
Gender (male)	0.057	1.059	0.757–1.480	0.738
Age (years)	0.036	1.037	1.021–1.053	<0.001*
BMI ( $>30 \text{ kg/m}^2$ )	0.071	1.074	0.807–1.429	0.626
Haplogroup H versus non-H	0.149	1.161	0.881–1.529	0.289

Soto-Hermida et al. *Rheumatology Int* 2014

## COHORTE PROCOAC

### Progresión radiológica en base a colocación de prótesis

**Table 3** Multivariate Cox regression analysis in patients who reached total joint replacement

*B* regression coefficient, *HR* hazard ratio, *CI* confidence interval, *BMI* body mass index

\* Statistical significance declared at  $p \leq 0.05$

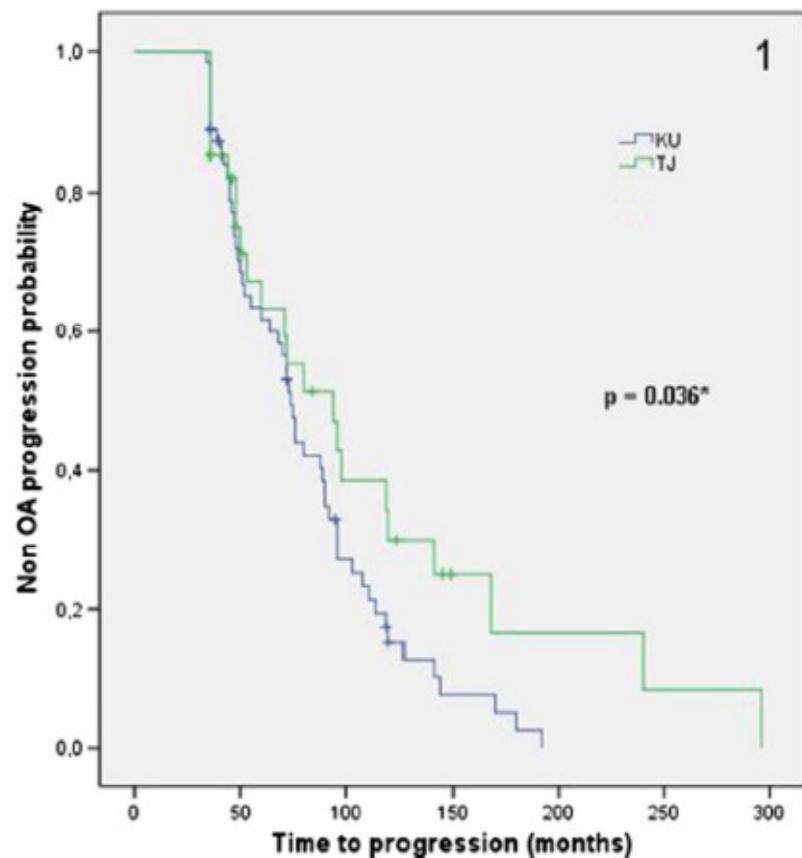
# This group includes both minor European haplogroups *I*, *W*, *X* and non-European

<sup>c</sup> *p* value from the Cox regression model

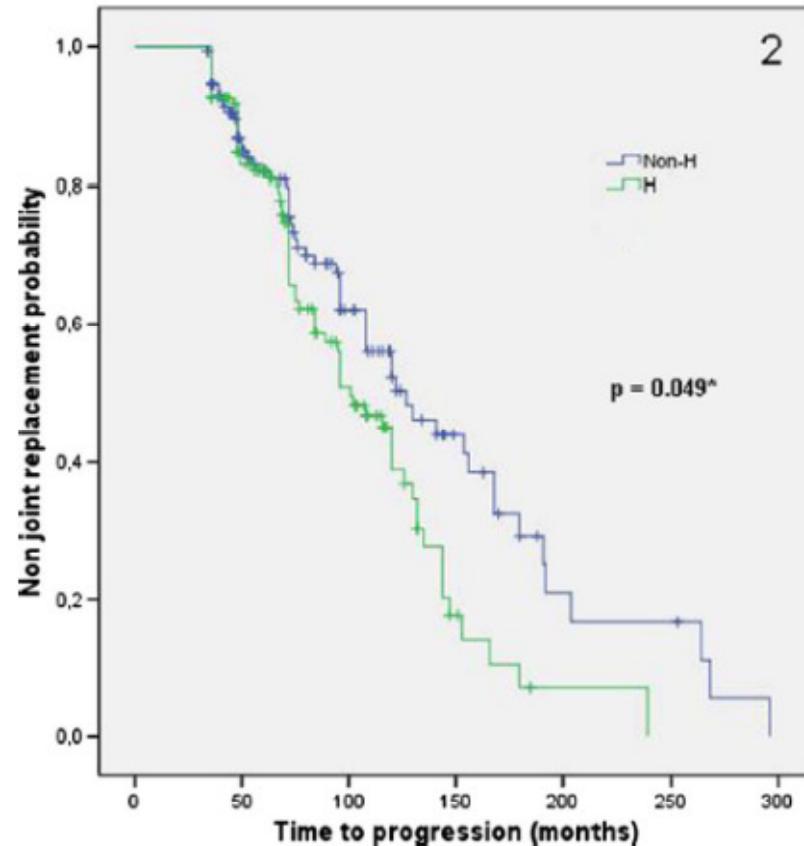
Variables	<i>B</i>	HR	95 % CI	<i>p</i> <sup>c</sup>
Analysis by mtDNA clusters				
Gender (male)	0.426	1.530	1.020–2.296	<b>0.040*</b>
Age (years)	0.060	1.062	1.039–1.085	<b>&lt;0.001*</b>
BMI ( $>30 \text{ kg/m}^2$ )	0.043	1.044	0.715–1.525	0.823
mtDNA clusters				0.796
HV versus TJ	0.278	1.320	0.739–2.357	0.348
KU versus TJ	0.276	1.318	0.682–2.548	0.412
Others <sup>#</sup> versus TJ	0.130	1.139	0.553–2.344	0.725
Analysis of mtDNA haplogroup H versus non-H				
Gender (male)	0.408	1.504	1.004–2.252	<b>0.048*</b>
Age (years)	0.058	1.060	1.037–1.082	<b>&lt;0.001*</b>
BMI ( $>30 \text{ kg/m}^2$ )	0.056	1.057	0.728–1.534	0.770
Haplogroup H versus non-H	0.366	1.441	1.002–2.073	<b>0.049*</b>

Soto-Hermida et al. *Rheumatology Int* 2014

# COHORTE PROCOAC



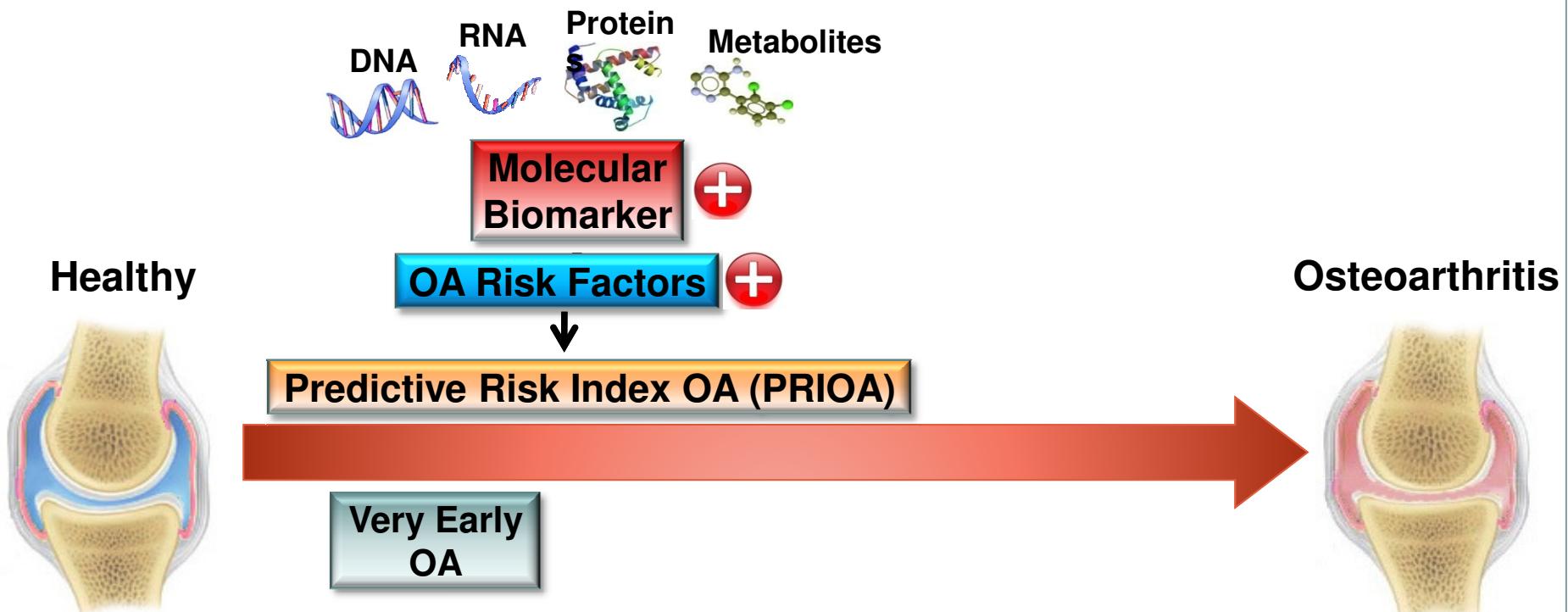
**Fig. 1** Kaplan-Meier survival curves for the radiographic progression of osteoarthritis (OA) showing the influence of mitochondrial clusters TJ and KU. (\*) Cox regression analysis



**Fig. 2** Kaplan-Meier survival curves for the radiographic progression of osteoarthritis (OA) in patients who reached total joint replacement showing the influence of mtDNA haplogroup H. (\*) Cox regression analysis

Soto-Hermida et al. *Rheumatology Int* 2014

# USO DE HERRAMIENTAS GENÉTICAS COMO INDICADORES DE PREDICCIÓN DE RIESGO DE ARTROSIS



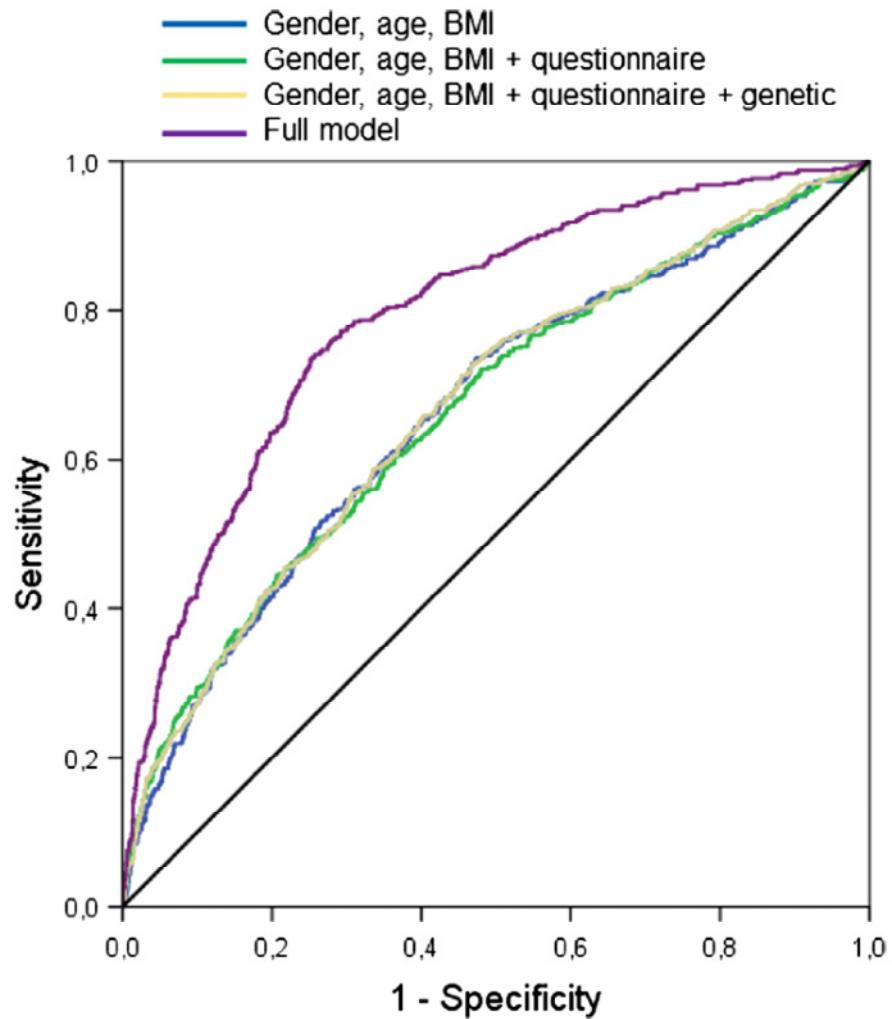
EXTENDED REPORT

## Prediction model for knee osteoarthritis incidence, including clinical, genetic and biochemical risk factors

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M Castano-Betancourt,<sup>1,2</sup> D J Hart,<sup>6</sup> A Hofman,<sup>7</sup> F Rivadeneira,<sup>1,2,7</sup> E H G Oei,<sup>8</sup>  
Tim D Spector,<sup>6</sup> A G Uitterlinden,<sup>1,2,7</sup> A C J W Janssens,<sup>7</sup> A M Valdes,<sup>6,9</sup>  
J B J van Meurs<sup>1,2</sup>

### Outcome assessment: incident KOA

In all studies, knee ROA was defined as a KL score  $\geq 2$  (= at least two definite osteophytes and possible joint space narrowing) of one or both joints. Incidence of knee ROA is defined as a KL score  $< 2$  at baseline and a KL  $\geq 2$  at follow-up (mean follow-up time is specified in table 1) of the same knee. We included individuals with unilateral KOA, since they were at risk of developing incident OA at the other knee.



**Figure 1** Receiver operating characteristic curves for the four risk prediction models as specified in table 1 for Rotterdam Study I. The fourth model includes also the radiographic variables. BMI, body mass index.



Rheumatology

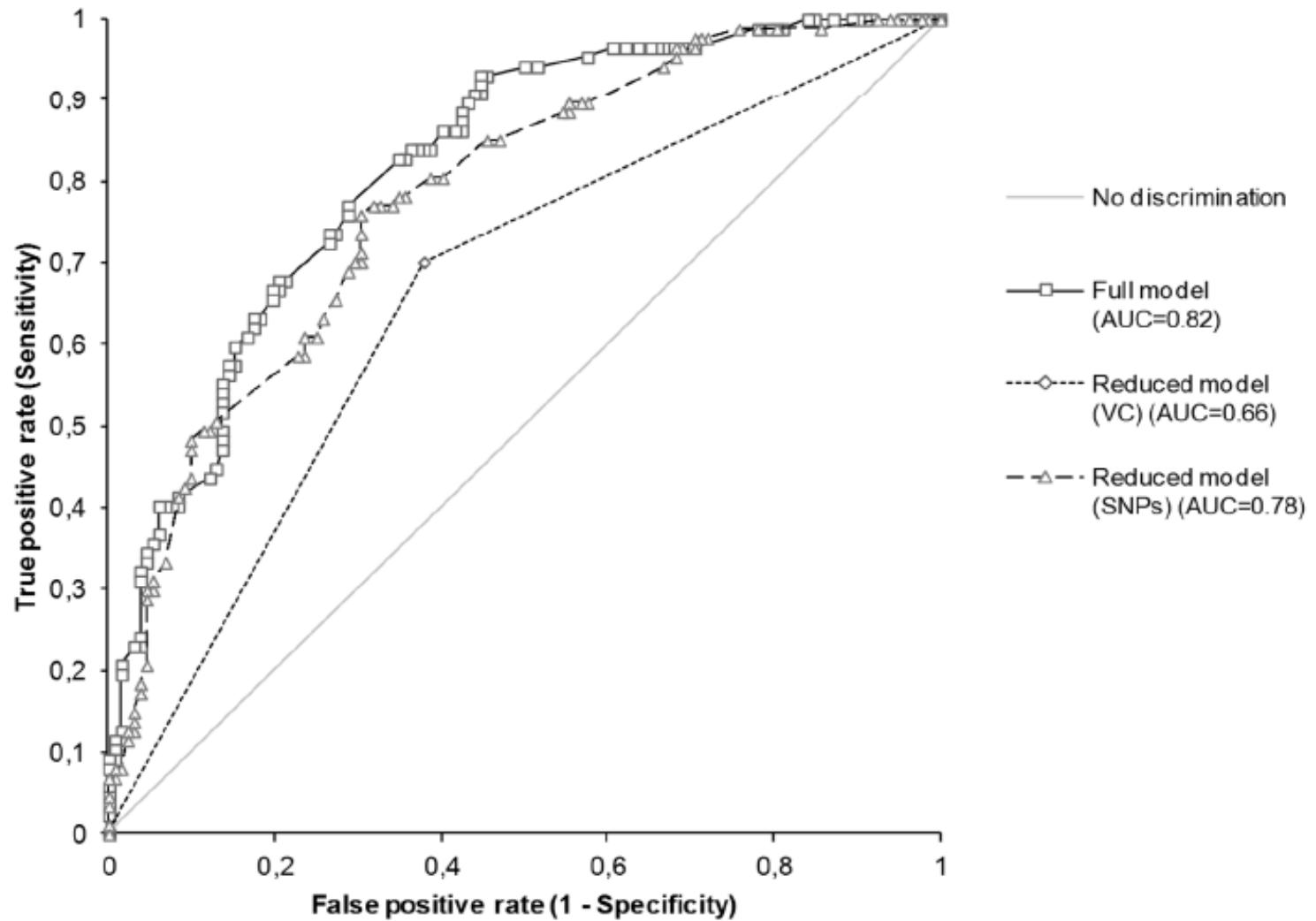
## **Improved prediction of knee osteoarthritis progression by genetic polymorphisms. The Arthrotest Study**



Journal:	<i>Rheumatology</i>
Manuscript ID:	Draft
Manuscript Type:	Original Article (includes systematic reviews)
Date Submitted by the Author:	n/a
Complete List of Authors:	Blanco Garcia, Francisco J; INIBIC-Complejo Hospitalario Universitario A Coruña, Aging and Inflammation Research Lab

**Table 2.** Multivariate logistic regression analysis to predict knee OA progression. The variables included in the full model and their OR (95% IC) and p-value are shown.

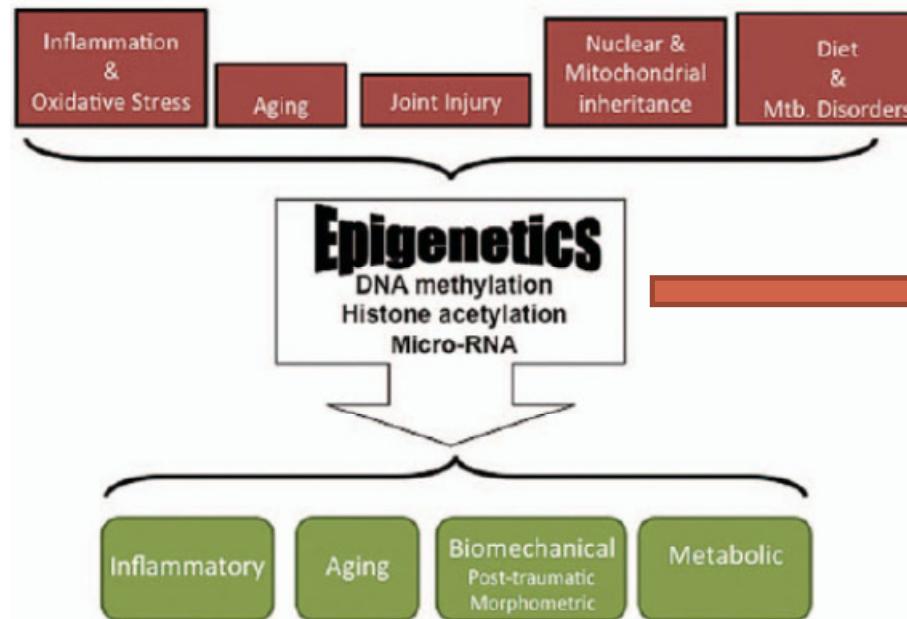
Variables (full model)	Chr	Gene	nt change	Risk allele	Risk genotype	OR (IC 95%)	p-value
Older age of OA onset						3.66 (1.87-7.17)	0.0002
rs2073508	5	<i>TGFB1</i>	C/T	C	CC	3.19 (1.58-6.46)	0.001
rs10845493	12	<i>LRP6</i>	A/G	A	AA +AG	2.78 (1.25-6.16)	0.012
rs2206593	1	<i>PTGS2(COX2)</i>	C/T	T	TT + TC	4.44 (1.39-14.23)	0.012
rs10519263	15	<i>near to SLC27A2</i>	C/T	C	CC +TC	2.08 (1.00-4.33)	0.050
rs874692	10	<i>CHST3</i>	A/G	G	GG	2.36 (1.17-4.77)	0.017
rs7342880	17	<i>TIMP2</i>	G/T	T	TT + TG	2.95 (1.06-8.22)	0.039
rs780094	2	<i>GCKR2</i>	C/T	C	CC + TC	2.53 (1.06-6.07)	0.037
rs12009	9	<i>GRP78(HSPA5)</i>	C/T	C	CC + TC	3.03 (1.35-6.80)	0.007



**Figure 1.** Multivariate models to predict knee OA progression. The full model combining SNPs and clinical variables and the reduced models combining only clinical variables or SNPs are shown.

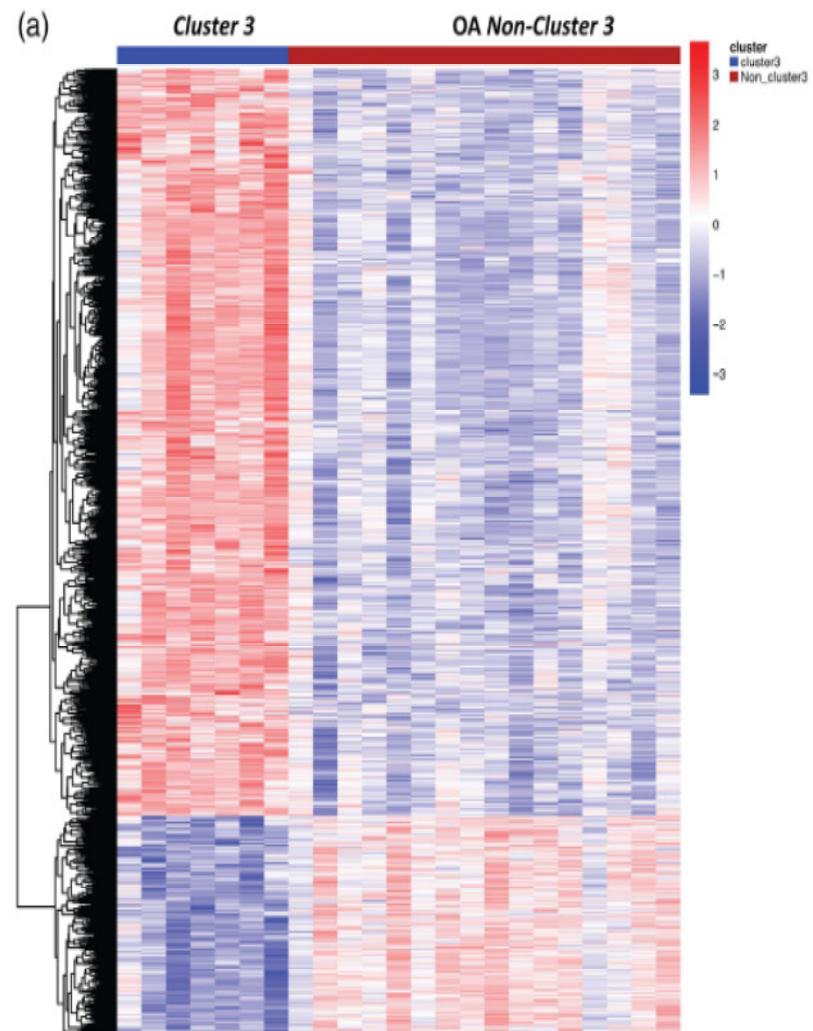
Blanco FJ et al. *Rheumatology* in press 2014

# Environmental Factors

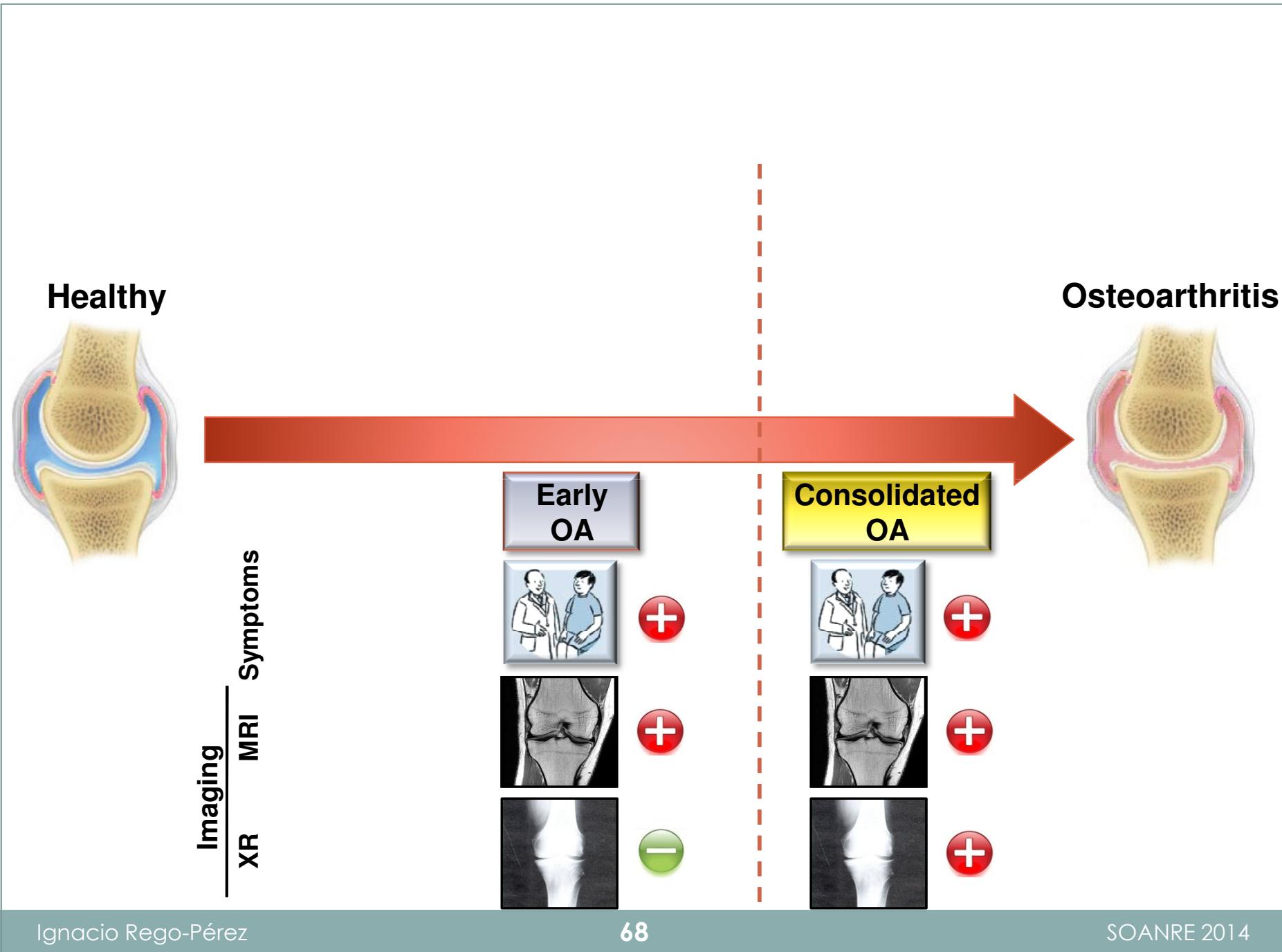


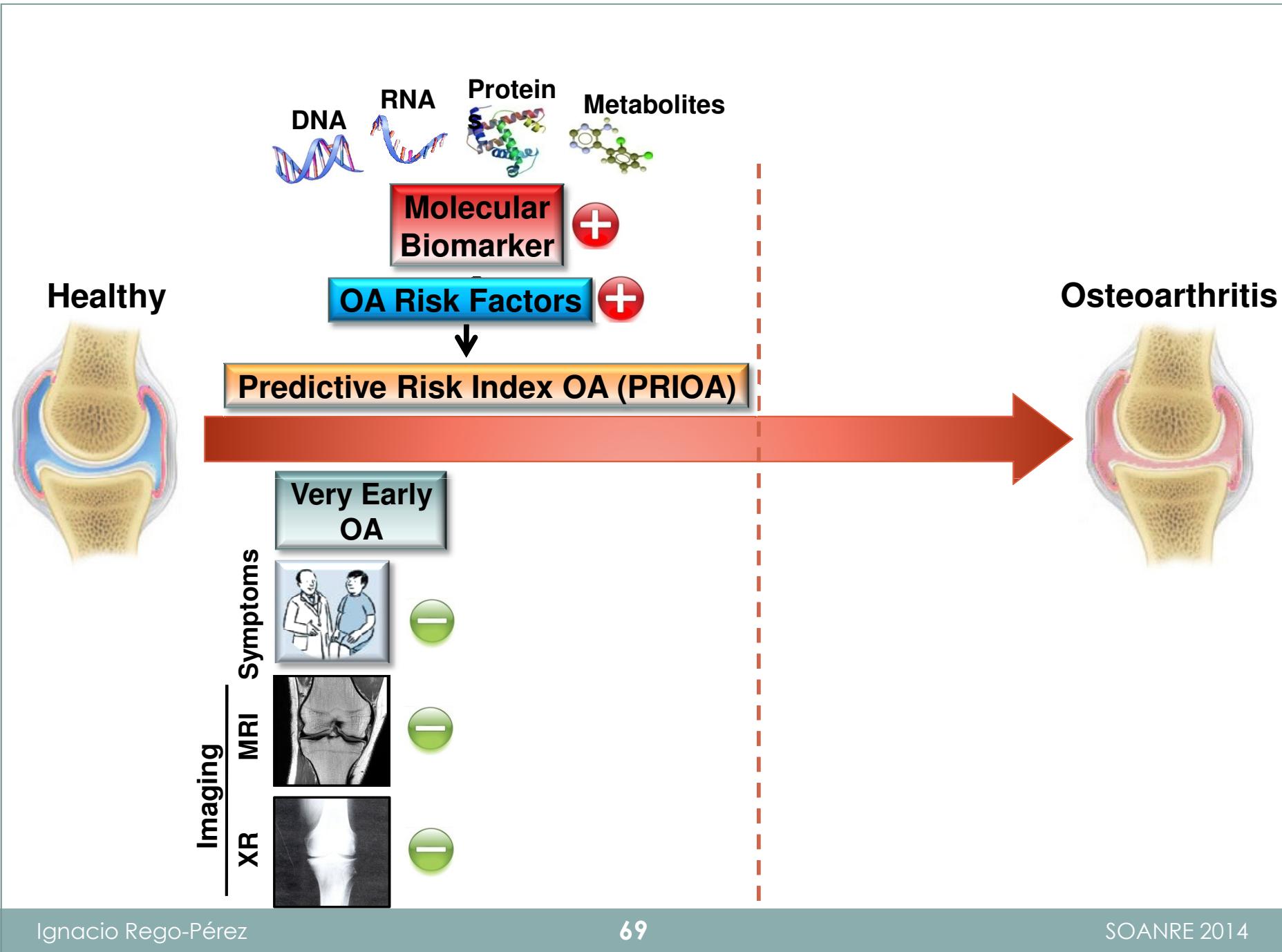
## Phenotype of OA

**Figure 1.** Association between epigenetics and osteoarthritis (OA) phenotypes. Different stimuli (environmental factors), such as joint injury, oxidative stress, and inflammatory cues, aging, diet, metabolic (Mtb.) disorders, or both nuclear and mitochondrial genetics are prone to alter the DNA methylome in OA, leading to the development of different phenotypes of OA.



Blanco FJ and Rego-Pérez I. *Arthritis Rheumatol* 2014





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